

H A N D B O O K O F

Pharmaceutical Manufacturing Formulations

Over-the-Counter Products

V O L U M E 5

Handbook of Pharmaceutical Manufacturing Formulations

Volume Series

Sarfaraz K. Niazi

Volume 1

*Handbook of Pharmaceutical Manufacturing Formulations:
Compressed Solid Products*

Volume 2

*Handbook of Pharmaceutical Manufacturing Formulations:
Uncompressed Solid Products*

Volume 3

*Handbook of Pharmaceutical Manufacturing Formulations:
Liquid Products*

Volume 4

*Handbook of Pharmaceutical Manufacturing Formulations:
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Volume 5

*Handbook of Pharmaceutical Manufacturing Formulations:
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Volume 6

*Handbook of Pharmaceutical Manufacturing Formulations:
Sterile Products*

H A N D B O O K O F
Pharmaceutical
Manufacturing
Formulations

Over-the-Counter Products

VOLUME 5

Sarfraz K. Niazi



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Dedication

Dedicated to the memory of Dean Allen I. White

Preface to the Series

No industry in the world is more highly regulated than the pharmaceutical industry because of the potential threat to a patient's life from the use of pharmaceutical products. The cost of taking a new chemical entity to final regulatory approval is a staggering \$800 million, making the pharmaceutical industry one of the most research-intensive industries in the world. It is anticipated that the industry will spend about \$20 billion on research and development in 2004. Because patent protection on a number of drugs is expiring, the generic drug market is becoming one of the fastest growing segments of the pharmaceutical industry with every major multinational company having a significant presence in this field.

Many stages of new drug development are inherently constrained by time, but the formulation of drugs into desirable dosage forms remains an area where expediency can be practiced by those who have mastered the skills of pharmaceutical formulations. The *Handbook of Pharmaceutical Manufacturing Formulations* is the first major attempt to consolidate the available knowledge about formulations into a comprehensive and, by nature, rather voluminous presentation.

The book is divided into six volumes based strictly on the type of formulation science involved in the development of these dosage forms: sterile products, compressed solids, uncompressed solids, liquid products, semisolid products, and over-the-counter (OTC) products. Although they may easily fall into one of the other five categories, OTC products are considered separately to comply with the industry norms of separate research divisions for OTC

products. Sterile products require skills related to sterilization of the product; of less importance is the bioavailability issue, which is an inherent problem of compressed dosage forms. These types of considerations have led to the classification of pharmaceutical products into these six categories. Each volume includes a description of regulatory filing techniques for the formulations described. Also included are regulatory guidelines on complying with Current Good Manufacturing Practices (cGMPs) specific to the dosage form and advice is offered on how to scale-up the production batches.

It is expected that formulation scientists will use this information to benchmark their internal development protocols and reduce the time required to file by adopting formulae that have survived the test of time. Many of us who have worked in the pharmaceutical industry suffer from a fixed paradigm when it comes to selecting formulations: "Not invented here" perhaps is kept in the back of the minds of many seasoned formulations scientists when they prefer certain platforms for development. It is expected that with a quick review of the formulation possibilities that are made available in this book such scientists would benefit from the experience of others. For teachers of formulation sciences this series offers a wealth of information. Whether it is selection of a preservative system or the choice of a disintegrant, the series offers many choices to study and consider.

Sarfaraz K. Niazi, Ph.D.
Deerfield, Illinois

Preface to the Volume

The *Handbook of Pharmaceutical Manufacturing Formulations: Over-the-Counter Products* is written for the pharmaceutical scientist and others involved in the regulatory filing and manufacturing of new OTC products. Because of the wide variety of products involved, from those bordering on cosmetics to proton pump inhibitors, the OTC products are manufactured by the most sophisticated global manufacturers as well as small one-room makeshift manufacturing houses.

The OTC products comprise a special category of healthcare products in that they can be dispensed without prescription, the rationale being that the use of these products does not expose patients to serious risks associated with side effects even if some misuse or overuse of these products occurs. The OTC category includes three types of products:

- Products that require full filing with the U.S. Food and Drug Administration (FDA) for marketing approval (the NDA/NADA or aNDA/aNADA process) including products or compositions not included in the monographs (see below) or administered in controlled release formulations
- Products that do not require filing with the U.S. FDA because they comply with the monographs issued by the U.S. FDA in its *Code of Federal Regulations* (CFR)
- Products that fall under the category of grandfather products which have been in use prior to the 1960s and have not been specifically excluded by the FDA; not all grandfather products fall under the OTC category — only those that are Generally Regarded As Safe (GRAS)

The U.S. FDA provides excellent support through its OTC website (<http://www.fda.gov/cder/otc/index.htm>) and formulators are highly encouraged to make use of the information available, particularly the updates in the monograph label requirements and withdrawal of approvals of formulations.

With the safety of consumers in mind, the U.S. FDA is in the process of establishing guidelines for all OTC products. Although the U.S. FDA began this work over three decades ago, much remains to be done. The U.S. FDA process begins with the issuance of Proposed Rules; this notification is like a warning (or advice) to the industry

that this category of products is now under U.S. FDA watch. Often years go by before Proposed Rules are published in the *Code of Federal Regulations*. The Proposed Rules include not only identification of approved active ingredients but also inactive ingredients that are deemed compatible with the active ingredients and safe for consumers. The Proposed Rules are subject to criticism by the industry healthcare practitioners and consumers. After receiving these comments over what can be a period of several years, the U.S. FDA issues Final Rules on a specific category of products; these become official on the date of publication in the *Code of Federal Regulations*. In many cases, however, the U.S. FDA issues subsequent rules either to delay application of Final Rules or to modify the Final Rules if new information has become available.

The Final Rule requirements have primarily been applied to products on the market and a newcomer is well advised to study competitor products for market leaders as ample opportunities are available to innovate these products. Examples include the Tylenol® Hot Therapy products and loratidine tablets that dissolve in the mouth and do not require water. I foresee more such products entering into the ever-competitive OTC market.

It is imperative that any prospective entry into the OTC market should begin with a thorough consultation of the Final Rules; an examination of Proposed Rules and notifications to issue Proposed Rules is also helpful in determining what rules are about to become Final Rules. Reviewing the discussions about Proposed Rules that have affected their finalization can be very helpful in understanding the relevant issues of safety, efficacy and labeling. Because the marketing of OTC products requires a large investment in marketing efforts, it is prudent to develop a clear understanding of the legality of formulations and claims made in the initial phases of product development.

A large number of products on the market today are not covered by the U.S. FDA monographs but does that make them legitimate? This is the often-asked question. The U.S. FDA has limited resources to tackle everything that is out there on the market. When emergencies arise, however, the U.S. FDA reacts immediately as it did in the case of phenylpropanolamine, pseudoephedrine and recently, kava kava. Here are some broad guidelines adopted by the U.S. FDA for the most commonly abused categories of products:

1. No treatments are approved for hair growth except for minoxidil.
2. No treatments are approved for enhancing sexual performance except for sildenafil citrate (and that only in MED).
3. The few treatments approved for weight loss include orlistat phentermine and sibutramine (phenylpropanolamine is no longer a recommended compound).

It is noteworthy that the U.S. FDA does not differentiate between botanical products and chemical-based products. If a product bears an efficacy claim it must be governed by U.S. FDA rules; however a product that falls into a drug category that makes nutritional claims falls under a food category with its own set of detailed rules. Vitamins and minerals fall under food labeling guidelines; however a single-entity vitamin product with specific claims to treat or ameliorate a disease is a drug product. These definitions do not necessarily coincide with the rulings of regulatory authorities worldwide. In many countries nutritional products are controlled as drugs and require prescriptions; these same products would be considered non-prescription items in the United States. On the other hand a number of highly active drugs are available without prescription in many countries such as the Traditional Chinese Medicine (TCM) in China and Ayurvedic and Unani medicines in South Asia.

A reclassification of a drug to OTC status can be requested by drug manufacturers. Recent examples of such a prescription-to-OTC switch include ibuprofen (200 mg), ranitidine hydrochloride (75 mg), and loratidine (10 mg). Note that specific strengths, not necessarily the chemical entity itself, are made OTC. In other words it is not necessary to have an official monograph to secure OTC status for a drug. The decision to request reclassification of a drug as OTC is always a well-calculated business decision. Generally drugs with an OTC status will not qualify for medical reimbursement by insurance companies or federal assistance programs in the United States. This can substantially reduce sales of the product; on the other hand, ease of availability to a greater number of patients can easily compensate for this loss. The most lucrative opportunities arise when one strength is made OTC while other strengths remain available by prescription only.

It is noteworthy that the decision to allow a switch from prescription to OTC by the U.S. FDA is primarily driven by the side effects or toxicity of the drug. For example, in Australia a Roche request for a prescription-to-OTC switch for its weight-loss drug orlistat (Xenical®) was recently turned down because of extensive side effects associated with the use of Xenical. The drug itself is very safe as it does not enter the body and acts only locally to partially block absorption of fat. The unabsorbed fat produces many

gastrointestinal symptoms which although temporary were sufficient to disallow the status switch. Obviously Roche would have been best advised to develop an OTC formulation with fewer side effects before requesting this switch. (In the case of orlistat, the solution was simple as described in U.S. Patent No. 6,251,421 by this author wherein combining orlistat with a natural fiber reduced the side effects by 70%.)

The OTC category of products represents a wide range of dosage forms. These formulations have much in common with their prescription counterparts but are presented in this volume of the *Handbook of Pharmaceutical Manufacturing Formulations* because of the development approach taken, labeling considerations, and support available from suppliers of ingredients in designing these products. Because the consumer is inevitably involved in the selection of these products, packaging considerations are much more important than in the prescription category of products. Additional considerations include ease of administration, palatability, and stability in storage as consumers are likely to keep leftovers around for a long time. Additionally, price constraints often make it difficult to enjoy some freedom of choice in formulations especially if the innovator company faces the competition of house brands. All of these considerations taken together make the OTC category one that should be presented in a single volume of this series of books.

Formulating OTC products is generally easier than formulating prescription products if the product is described in U.S. FDA monographs (either as Proposed Rules or Final Rules); such formulations become merely an exercise in mechanics. Whereas a manufacturer is not bound by these rules, complying with them reduces the costs and time involved securing approval from regulatory authorities. The multibillion-dollar market of OTC products has attracted major chemical suppliers to develop support ingredients that are much easier to use; they have also developed typical formulations for hundreds of these products.

The most notable industry leaders include:

- Amerchol
- American Colloid
- Aqualon
- BASF
- BF Goodrich
- Calgon
- Colorcon
- Croda
- Dow Corning
- FMC
- Gattefosc
- General Electric
- Henkel
- Hormel

- Huls America
- ICI Americas
- Inolex
- International Sourcing
- International Specialty
- Laboratoires Serobiologique
- Lonza
- NIPA
- PPG Industries
- R.I.T.A.
- Reheis
- Rheox
- Rhone-Poulenc
- Rohm and Haas
- Southern Clay
- Sutton
- Vanderbilt

The formulations recommended by these and other companies have acquired almost a universal appeal; throughout this book you will find formulations recommended by these laboratories, as acknowledged by the listing of a brand name in the formula. The best way to connect to these companies is to search the Internet for contact information; it is no longer necessary to reproduce such information here. Whereas many companies prefer to use generic components in the dosage form, it has been found that the use of proprietary components can indeed reduce costs in the long run.

The choice of color is a highly sensitive issue in the formulation of OTC products; only FD&C colors are allowed. Whereas there is a great need to make the products attractive and appealing, the choices of safe colors are dwindling quickly, such as for red colors. The formulator is encouraged to review the status of approved colors around the world before committing to a specific color.

Many OTC solid dosage forms are available in coated form. Sugar coatings have yielded to film coatings, and this book contains a large number of sugar-coating, seal-coating, subcoating, film-coating, and polish-coating formulations that can be easily adapted to various dosage form sizes. The use of organic solvent-based coatings has become prohibitive because of environment considerations, but in those cases where formulations are extremely sensitive to moisture, organic coatings may still offer a valid choice. A few companies offer ready-made coating formulations, and these are worth considering. The Appendix to this book includes a large number of formulations of coatings of solid dosage forms. A keen formulator will have no difficulty based on these formulations in adopting a coating system that will provide the necessary protection and offer esthetic appeal as well. Solid dosage forms are coated for many reasons, including masking the taste, making them easier to swallow, and providing protection against the environment.

Stability considerations remain paramount, and the data in the final packaging must be evaluated carefully before adjusting formulae for excesses; in this book, most formulations are provided without this consideration. A strip or blister dosage form is more popular around the world, but the plastic bottle is the most popular final form in the United States.

The development of OTC products is similar to the development of prescription dosage forms; as a result, cGMP and Good Laboratory Practice (GLP) considerations apply equally. The first chapter describes in greater detail the cGMP considerations. An Appendix to Chapter 1 provides a comprehensive checklist of items to review to ensure that a manufacturing facility is in compliance with cGMP standards. Appropriate identification is made in this checklist of those items that comply with EC guidelines. The U.S. FDA guidelines are available from the U.S. FDA website: <http://www.fda.gov>. The World Health Organization (WHO) provides GMP guidelines that are less stringent than those of the U.S. FDA and EC, and formulators should be aware of the fact that all of these are simply *guidelines*. One should be fully cognizant of the fact that no agencies are bound by these guidelines, particularly the U.S. FDA. Manufacturers cannot take refuge in the defense that they have complied with these guidelines. It is further worthwhile remembering that all of these guidelines are continuously revised, and the “c” in the cGMP does refer to *current*.

The second chapter deals with the most popular category of dosage forms encountered in OTC offerings — solids. Issues specific to manufacturing of these dosage forms are described from a practical viewpoint, indicating the problem areas frequently encountered in manufacturing practice.

The third chapter deals with liquids and suspensions and includes, like the chapter above, practical advice on how to bring manufacturing practices into compliance with regulatory requirements.

The fourth chapter offers highlights of cleaning validation, a topic often ignored by OTC manufacturers as not being significant because of the safety of ingredients used. It is true that the same stringent standards may not apply, but compliance with cleaning standards and validation of processes go a long way toward ensuring overall compliance.

The first four chapters were drawn from advice the U.S. FDA gives to its inspectors before they inspect a manufacturer. The CFR includes complete details of what is considered acceptable by the U.S. FDA; this advice is of a practical nature, and I find it to be extremely helpful in enhancing awareness of the guidelines of regulatory authorities. It is noteworthy that EC guidelines, particularly in light of the harmonization of specifications, are somewhat identical to the U.S. FDA guidelines; in chapter 1, specific references are made to EC guidelines. The

Appendix includes formulations of coating solutions; these should prove useful for the pharmaceutical formulation teams.

The formulations in this book generally fall into three categories. Some formulations are presented in greater detail, including indications of where quality assurance (QA)/quality control (QC) sampling is to be done and describing the tooling and in-process and finished product specifications. The other extreme is a mere listing of components with a bare minimum of manufacturing methods. This was necessary for two reasons: first, to contain the size of this book, and, second, to keep from presenting superfluous information, as formulators would eventually adopt such a formula to their own delivery forms. Also, at times the various strengths are merely achieved through adjustment of dosage size, so it was considered unnecessary to reproduce manufacturing steps where they are obvious.

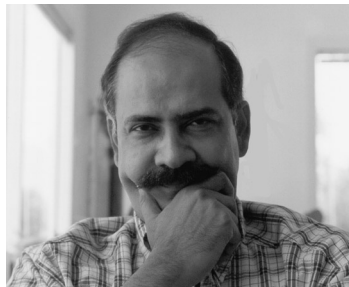
The primary source of these formulations is publicly available knowledge about formulae that have proven to provide stable products. No representation is made that these formulations meet U.S. FDA monographs or any other regulatory guidelines for safety of inert ingredients. The formulator is advised to determine guideline compliance before adopting any of the formulations given in this book. Those interested in obtaining detailed information about these formulations are encouraged to contact the author at

<http://www.pharmsci.com>. Because of the wide variety of sources from which the information has been gathered in the book, the format of formulations also varies. For example, in some instances scale is provided, whereas in others a percentage by weight is described. In still other instances, quantities for a specific batch size are provided. Obviously, it would be desirable to convert these formulations into a uniform format, but the task would be daunting and inevitably would lead to inclusion of errors. Professional formulators should not encounter any difficulty in adapting these formulations to their own system.

As mentioned before, not all formulations contain the required overages for stability considerations and losses during manufacturing; formulators are expected to develop these based on the final packaging chosen for the product. The author would appreciate being notified of any special problems encountered in adopting these formulations or of any errors (niazi@pharmsci.com). Whereas much care has gone into ensuring the accuracy of quantities and proper identification of ingredients, such errors shall remain in a work as large as that presented here.

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About the Author



Dr. Sarfaraz K. Niazi has been teaching and conducting research in the pharmaceutical industry for over 30 years. He has authored hundreds of scientific papers, textbooks, and presentations on the topics of pharmaceutical formulation, biopharmaceutics, and pharmacokinetics of drugs. He is also an inventor with scores of patents and is licensed to practice law before the U.S. Patent and Trademark Office. Having formulated hundreds of products from consumer products to complex biotechnology-derived products, he has accumulated a wealth of knowledge in the science of formulations and regulatory filings of Investigational New Drugs (INDs) and New Drug Applications (NDAs). Dr. Niazi advises the pharmaceutical industry internationally on issues related to formulations, pharmacokinetics and bioequivalence evaluation, and intellectual property issues (<http://www.pharmsci.com>).

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Many have assisted me in the development of this work that has taken years to compile, and I am thankful to scores of my graduate students and colleagues for their help.

The diligent and ardent editorial support offered by CRC Press was exemplary; nevertheless, any remaining errors are altogether mine. I am grateful to CRC Press for taking this lead in publishing what is possibly the largest such work in the field of OTC products. It has been a distinct privilege to have known Stephen Zollo, a Senior Editor at CRC Press, for many years. The editorial assistance provided by CRC Press staff was indeed exemplary, particularly the help given by Erika Dery, Susan Fox, and others.

I have dedicated this book to Dean Allen I. White, whom I met in 1970 when I began my graduate work at the Washington State University (WSU) in Pullman. Until his death last December, we stayed in touch, and I continued to benefit from his advice and kindness. He served as Dean of the WSU College of Pharmacy for 19 years. With a distinct lean disposition and straightforward approach to the profession he loved and the life he cherished, he taught us many things. I am so fortunate to have had this opportunity to know such a great educator, scientist, and leader.

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Calamine Cream
Calamine Cream
Calamine Lotion
Calcium and Vitamin D Tablets
Calcium Carbonate and Glycine Tablets

Calcium Carbonate and Vitamin D Tablets
Calcium Carbonate Tablets
Calcium D-Pantothenate Chewable Tablets
Calcium D-Pantothenate Tablets
Calcium D-Pantothenate Tablets
Calcium Effervescent Tablets
Calcium Gluconate Tablets
Calcium Glycerophosphate Tablets
Calcium Glycerophosphate Tablets
Calcium Iodide and Ascorbic Acid Syrup
Calcium Phosphate Tablets for Cats and Dogs (Direct Compression)
Calcium Phosphate Tablets for Cats and Dogs
Carbinoxamine Maleate, Phenylpropanolamine, and Acetaminophen Sustained-Release Tablets
Carbonyl Iron, Copper Sulfate, and Manganese Sulfate Tablets
Carnitine and Coenzyme Q Solution
Cetrimide Antiseptic Cream
Charcoal Tablets
Chlophedianol, Ipecac, Ephedrine, Ammonium Chloride, Carbinoxamine, and Balsam Tolu Syrup
Chlorhexidine Gel
Chlorhexidine Lozenges
Chlorpheniramine Maleate Syrup
Chymotrypsine Tablets
Citrate Effervescent Powder
Crospovidone Effervescent Tablets
Crospovidone Water Dispersible Tablets
Cyanocobalamin Tablets
Dexpanthenol Gel-Cream
Dextromethorphan, Pseudoephedrine, and Chlorpheniramine Maleate Syrup
Dihydroxyaluminum Sodium Carbonate Tablets
Dimenhydrinate Tablets
Dimenhydrinate Tablets
Dimenhydrinate Tablets
Diphenhydramine Hydrochloride Tablets
Econazole Nitrate and Benzoyl Peroxide Anti-Acne Cream
Econazole Nitrate and Benzoyl Peroxide Anti-Acne Lotion
Eucalyptol Solution
Eucalyptus and Mint Emulsion
Eucalyptus and Mint Ointment
Ferrous Fumarate Tablets
Ferrous Sulfate, Manganese Sulfate, and Copper Sulfate Tablets
Ferrous Sulfate Oral Solution
Ferrous Sulfate Oral Syrup
Ferrous Sulfate Tablets
Fir Needle Oil Solution
Folic Acid Tablets
Folic Acid Tablets
Foot Bath
Foot Freshener Cream
Foot Mousse
Garlic Tablets
Glycerin Suppositories
Glycerin Suppositories for Children
Glycol Foam, Nonaqueous
Guaifenesin Pseudoephedrine, Carbinoxamine, and Chlophedianol Drops
Hemorrhoid Cream

Horsetail Extract Tablets
Hydrocortisone Aqueous Gel
Hydrocortisone Aqueous Gel
Hydrocortisone Cream
Hydrocortisone Cream
Hydrocortisone Ethanolic Gel
Hydrocortisone Ointment
Ibuprofen Pediatric Suspension
Ibuprofen Tablets
Inosin Tablets
Insect Bite Cream
Iron (Polymer Coated Particle) Tablets
Iron Infant Drops
Iron Polystyrene and Vitamin C Syrup
Kaolin–Pectin Suspension
Kaolin–Pectin Tablets
Keratolytic Cream
Khellin Tablets
Lidocaine Gel
Lidocaine Gel–Cream
Lidocaine Ointment
Lidocaine, Eugenol, and Menthol Dental Ointment
Loratidine Tablets
Loratidine Fastab
Magaldrate Chewable Tablets
Magaldrate Dispersible Tablets
Magaldrate Instant Powder or Dry Syrup
Magaldrate Suspension
Magaldrate Tablets
Magaldrate with Simethicone Suspension
Magaldrate with Simethicone Tablet
Magnesium Carbonate Tablets
Medicated Foot Cream
Methyl Salicylate Heat Rub Lotion
Methyl Salicylate Analgesic Cream
Methyl Salicylate Analgesic Cream
Methyl Salicylate and Menthol Gel
Metoclopramide Tablets
Miconazole Nitrate Cream
Mineral and Multivitamin Syrup
Mint-Menthol Mouthwash
Menthol Mouthwash
Mint Oil Solution
Multivitaminm, Calcium, and Iron Tablets
Multivitamin and Calcium Syrup
Multivitamin and Carbonyl Iron Tablets
Multivitamin and Mineral Tablets with Beta Carotene
Multivitamin and Mineral Syrup
Multivitamin and Mineral Tablets
Multivitamin Chewable Tablets for Children
Multivitamin Drops
Multivitamin Effervescent Granules
Multivitamin Effervescent Tablets with Beta Carotene
Multivitamin Effervescent Tablets
Multivitamin Effervescent Tablets

Multivitamin Infant Drops
Multivitamin Infant Drops
Multivitamin Instant Granules
Multivitamin Mineral Syrup
Multivitamin Oral Gel with Linoleic and Linolenic Acid
Multivitamin Oral Gel Veterinary
Multivitamin Syrup
Multivitamin Syrup
Multivitamin with Beta-Carotene Tablets
Multivitamin Tablets with Beta-Carotene
Multivitamin and Beta-Carotene Tablets
Multivitamin Tablets
Multivitamin Tablets
Multivitamin Tablets
Multivitamin Tablets
Multivitamin Tablets
Multivitamin Tablets for Dogs
Multivitamin and Fluoride Chewable Tablets
Multivitamin with Fluoride Infant Drops
Multivitamin with Zinc Tablets
Naphazoline Eye Drops
Neomycin Gel
Nicotinamide Tablets
Nicotinic Acid (Niacin) Tablets
Nondetergent Neutral Dry Skin Cream
Norephedrine Syrup
Nystatin Cream
Nystatin Ointment
Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Cream
Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Ointment
Omega Fatty Acids Tablets
Oral Rehydration Salt (45 mEq)
Pancreatin Tablets
Pancreatin Tablets
Pancreatin and Cholic Acid Tablets
Panthenol Lotion
Panthenol Ointment
Peppermint Rub Cream
Phenindion Tablets
Phenolphthalein Tablets
Phenolphthalein Tablets
Phenylpropanolamine Hydrochloride Tablets
Phenylpropanolamine, Chlorpheniramine, Dextromethorphan, Vitamin C Syrup
Placebo Tablets
Polidocanol Wound Spray
Polyvinylpyrrolidone–Iodine Mouthwash
Povidone–Iodine and Lidocaine Gel
Povidone–Iodine Bar Soap
Povidone–Iodine Bar Soap
Povidone–Iodine Bar Soap
Povidone–Iodine Concentrates for Broilers and Cattle
Povidone–Iodine Cream
Povidone–Iodine Effervescent Vaginal Tablets
Povidone–Iodine Foam Spray
Povidone–Iodine Gargle

Povidone–Iodine Gargle Solution Concentrate
Povidone–Iodine Gel-Cream
Povidone–Iodine Gels
Povidone–Iodine Glucose Ointment
Povidone–Iodine Liquid Spray
Povidone–Iodine Lozenges
Povidone–Iodine Mastitis Cream for Cattle
Povidone–Iodine Mouthwash and Gargle Solution Concentrate
Povidone–Iodine Powder Spray
Povidone–Iodine Pump Spray
Povidone–Iodine Shampoo
Povidone–Iodine Soft Gel
Povidone–Iodine Solution
Povidone–Iodine Solution
Povidone–Iodine Solution
Povidone–Iodine Solution
Povidone–Iodine Solution
Povidone–Iodine Scrub
Povidone–Iodine Surgical Scrub
Povidone–Iodine Surgical Scrub
Povidone–Iodine Transparent Ointment
Povidone–Iodine Vaginal Douche Concentrate
Povidone–Iodine Vaginal Ovule
Povidone–Iodine Vaginal Ovule
Povidone–Iodine Viscous Solution
Promethazine Hydrochloride Syrup
Promethazine Hydrochloride Tablets
Pseudoephedrine Hydrochloride Capsules
Pseudoephedrine Hydrochloride Syrup
Pseudoephedrine Hydrochloride Tablets.
Pseudoephedrine Tablets
Pseudoephedrine Hydrochloride, Carbinoxamine Maleate Oral Drops
Psoriasis Cream
Psoriasis Cream
Pyridoxine Tablets
Pyridoxine Tablets
Pyridoxine Tablets
Pyridoxine Tablets
Pyridoxine Tablets
Pyridoxine Tablets
Ranitidine Tablets
Ranitidine Hydrochloride Tablets
Riboflavin Tablets
Riboflavin Tablets
Riboflavin Tablets
Riboflavin Tablets
Riboflavin Tablets
Rubefacient Analgesic Ointment
Saccharin Effervescent Tablets
Saccharin Tablets
Saccharin Tablets
Salicylic Acid Cream
Selegiline Tablets
Selenium Sulfide Shampoo with Conditioner
Serratio Peptidase Tablets

Silicone Protective Cream
Silimarin Tablets
Simethicone Chewable Tablets
Simethicone Chewable Tablets
Simethicone Tablets
Sodium Fluoride Tablets
Sodium Fluoride Tablets
Spirulina Extract Chewable Tablets
Sucralfate and Sodium Alginate Tablets
Sulfur Antiseptic Ointment
Tannin–Crospovidone Complex Tablets
Tetrahydrozoline Eye Drops
Thiamine and Caffeine Tablets
Thiamine Hydrochloride Tablets
Thiamine Hydrochloride Tablets, Sugar-Coated
Thiamine, Pyridoxine, and Cyanocobalamine Tablets
Thiamine, Pyridoxine, and Cyanocobalamine Tablets
Thiamine, Pyridoxine, and Cyanocobalamine Tablets
Thiamine, Pyridoxine, and Cyanocobalamine Tablets
Thiamine, Pyridoxine, and Cyanocobalamine Tablets
Thiamine Tablets
Thiamine Tablets
Thiamine Tablets
Thiamine Tablets
Thiamine Tablets
Tolnaftate and Undecylanate Foot Care Cream
Tolnaftate Foot Care Microemulsion
Tolu Balsam Cough Syrup
Triclosan and Zinc Foot Deodorant Powder
Triclosan Foot Care Cream
Triprolidine and Pseudoephedrine Hydrochloride Syrup
Triprolidine and Pseudoephedrine Hydrochloride Tablets
Trolamine Salicylate Cream
Ultrasonic Adhesive Gel
Urea Peroxide Ear Drops
Valeriana and Passiflora Extract Tablets
Vitamin A and Vitamin D Infant Drops
Vitamin A and Vitamin D3 Drops
Vitamin A and Vitamin D3 Oral Solution
Vitamin A and Vitamin D3 Syrup
Vitamin A and Vitamin E Drops
Vitamin A and Vitamin E Drops (25,000 IU/50 mg/mL)
Vitamin A and Vitamin E Tablets
Vitamin A Chewable Tablets
Vitamin A Concentrate, Water-Miscible
Vitamin A Drops
Vitamin A Suppositories
Vitamin A Tablets
Vitamin A Tablets
Vitamin A Tablets
Vitamin A Tablets
Vitamin A Tablets
Vitamin A, Vitamin B6, and Vitamin E Tablets
Vitamin A, Vitamin C, and Vitamin D3 Chewable Tablets
Vitamin A, Vitamin C, and Vitamin E Tablets (1200 IU/60 mg/30 mg)

Vitamin B-Complex, Amino Acids, and Magnesium Effervescent Granules (Sugar-Free)
Vitamin B-Complex and Carnitine Tablets
Vitamin B-Complex and Folic Acid Dragees
Vitamin B-Complex and Iron Syrup
Vitamin B-Complex and Vitamin C Effervescent Tablets
Vitamin B-Complex and Vitamin C Instant Granules
Vitamin B-Complex and Vitamin C Syrup
Vitamin B-Complex and Vitamin C Syrup
Vitamin B-Complex and Vitamin C Tablets
Vitamin B-Complex and Vitamin C Tablets
Vitamin B-Complex, Choline, and Bile Tablets
Vitamin B-Complex Syrup
Vitamin B-Complex Syrup
Vitamin B-Complex Syrup (without B12)
Vitamin B-Complex Tablets
Vitamin B-Complex Tablets
Vitamin B-Complex Tablets
Vitamin B-Complex, Vitamin A, Vitamin C, and Vitamin D Syrup
Vitamin B-Complex, Vitamin A, Vitamin C, and Vitamin D Tablets
Vitamin B-Complex, Vitamin A, Vitamin C, Vitamin D, and Calcium Drops
Vitamin B-Complex, Vitamin A, Vitamin C, Vitamin D, and Mineral Tablets
Vitamin B-Complex, Vitamin A, Vitamin C, Vitamin D, and Vitamin E Pediatric Drops
Vitamin B-Complex, Vitamin C, and Calcium Effervescent Tablets
Vitamin B-Complex, Vitamin C, and Ferrous Sulfate Tablets
Vitamin B-Complex, Vitamin C, and Iron Syrup
Vitamin B-Complex, Vitamin C, and Iron Syrup
Vitamin B-Complex, Vitamin C, and Vitamin E Tablets
Vitamin C and Calcium Carbonate Effervescent Tablets (500 mg/300 mg)
Vitamin C and Vitamin E Lozenges
Vitamin C Chewable Tablets
Vitamin C Chewable Tablets
Vitamin C Chewable Tablets
Vitamin C Chewable Tablets
Vitamin C Chewable Tablets
Vitamin C Chewable Tablets with Dextrose
Vitamin C Chewable Tablets with Fructose
Vitamin C Chewable Tablets with Sucrose
Vitamin C Drops
Vitamin C Effervescent Tablets
Vitamin C Effervescent Tablets
Vitamin C Effervescent Tablets
Vitamin C Effervescent Tablets
Vitamin C Tablets
Vitamin C Tablets
Vitamin C Tablets
Vitamin E and Benzocaine Solution
Vitamin E Chewable Tablets
Vitamin E Chewable Tablets
Vitamin E Chewable Tablets
Vitamin E Concentrate, Water-Miscible
Vitamin E Drops
Vitamin E Gel-Cream
Vitamin E Softgel Capsules
Vitamin E Solution with Ethanol
Vitamin E Tablets

Vitamin E Tablets.
Zinc Oxide Lotion
Zinc Oxide Ointment
Zinc Pyrithione Shampoo
Zinc Undecylenate Cream
Zirconium Oxide Lotion

Part III

Appendix

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 - B. Cherry Red
 - C. Geranium Rose
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 - I. Holberry Red
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 - K. Opadry Yellow
 - L. Opadry Yellow
 - M. Opadry Red
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 - O. White Coating
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 - B. Red Mahogany
 - C. Sun Orange
 - D. Dark Red
 - E. Deep Yellow
 - F. Pale Yellow
 - G. Scarlet Red
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 - A. White
- V. Hydroxypropyl Methyl Cellulose/Ethyl Cellulose Coating
 - A. Reddish Orange Opaque
 - B. Subcoating Solution
- VI. Hydroxy Methyl Cellulose/Hydroxy Cellulose Coating
 - A. Blue
 - B. Clear (50:50)
- VII. Hydroxy Methyl Cellulose/Ethyl Cellulose Coating
 - A. Clear
- VIII. Polyvinylpyrrolidone (PVP) Coatings
 - A. Subcoating
 - B. Kollidon® VA 64 (Polyvinylpyrrolidone/Vinylacetate Copolymer, BASF)
 - C. Kollidon® VA 64 and Polyvinyl Alcohol
 - D. Kollidon® 30 and Shellac
 - E. Kollidon® VA 64 and Hydroxypropyl Methyl Cellulose
 - F. Povidone, Ethyl Cellulose, and Talc

- IX. Cellulose Acetate Phthalate and Carbowax Coatings
 - A. Brite Green
 - B. Cherry Red
 - C. Clear
 - D. Orange
 - E. Red Mahogany
 - F. Orange
- X. Sugar Coatings
 - A. Basic
 - B. Automatic
 - C. Manual, White
- XI. Enteric Coatings
 - A. Kollicoat® and Kollidon® Enteric Film Coating
- XII. Eudragit® Enteric Aqueous
 - A. Brick Red
 - B. Yellow
 - C. Brown
 - D. Dark Orange
 - E. Orange
 - F. Dispersed Orange
- XIII. Hydroxypropyl Methyl Cellulose Phthalate Enteric Coating
 - A. Clear Enteric
 - B. Orchid Pink Opaque
 - C. Light Apricot Orange

Part III

Appendix

Appendix: Coating Solutions

I. INTRODUCTION

Solid dosage forms are frequently coated for varied purposes, including:

- Mask taste and smell.
- Offer protection from the environment.
- Provide protection from gastric acid (enteric coating).
- Make dose easy to swallow.
- Provide identification.
- Add esthetic appeal.
- Hide surface defects.

Many types of coatings are available. A sugar coating used to be the preferred choice years ago; this type of coating has mostly been replaced with film coating, as new polymers with better film forming properties and equipment to apply these coatings have become available. Several proprietary coating formulations are also available, such as:

- Eudragit® (<http://www.rohmamerica.com/Eudragit/HomePage.html>)
- Colorcon® (http://www.colorcon.com/pharma/film_coat/index.html)

The advantage of using these prepackaged formulations is consistency in color matching, as well as other considerations regarding ease of use. The basic components of a film coating system are:

- Polymer
- Solvent
- Plasticizer
- Other ingredients
 - Anti-tack agent
 - Antifoam agent
 - Colorant
 - Filler/extender
 - Flavor
 - Surfactant

The following polymeric materials form the basis of most currently available coating formulations:

- Cellulose-based
 - Cellulose acetate phthalate (CAP)

- Hydroxypropyl methyl cellulose (HPMC)
- Hydroxypropyl cellulose (HPC)
- Hydroxypropyl ethyl cellulose
- Ethyl cellulose
- Methyl cellulose
- Microcrystalline cellulose and carageenan
- Methacrylic acid/methacrylate esters
 - Anionic and cationic polymers of methacrylic acid
 - Copolymers of methacrylates
 - Copolymers of acrylate and methacrylates
 - Copolymers of ethacrylate and methylmethacrylate
- Polyvinylacetatephthalate
- Shellac
- Polyvinylpyrrolidone

The choice of a coating formulation, ranging from a clear coat to a multilayered coating, depends to a great degree on the purpose of coating, such as protecting highly sensitive vitamins from oxidative degradation.

This book has provided several prototype formulations that can be readily adapted for the formulations provided here. The most significant aspect remains the choice of colors, which often determines the method of manufacturing the coating solutions. With a limited choice of dyes and lakes available for selection, manufacturers often use a combination of several colors and dyes along with agents such as talc for opaqueness to obtain the desired color and protection.

Another choice confronting manufacturers is whether to use an aqueous coating or an organic coating system; both have their advantages and disadvantages. Whereas organic coatings provide greater protection against moisture uptake during the coating process (important for moisture-sensitive ingredients) and are easier to apply because of the fast evaporation of solvents, problems encountered with these coatings include environmental control of organic solvents going into the atmosphere, the need to perform solvent residue tests, and the need to have explosion-proof facilities, thus aqueous coating systems are often preferred. In recent years, many developments in the formulation of aqueous coatings have made them an almost universally accepted mode of application.

Caution: Check with regulatory authorities about approved states of all dyes before using them.

II. HYDROXYPROPYL METHYLCELLULOSE (METHOCEL, HPMC) AQUEOUS COATINGS

Methocel-based coatings in an aqueous base are the most popular coating options; two methods of making solutions

are possible. If a lake is used, then alcohol is also included (see, for example, Holberry Red).

A. Brite Rose

Bill of Materials			
Scale (% w/v)	Item	Material Name	Quantity/L
6.00	1	Hydroxypropyl methylcellulose 2910 (15 cps)	60.00 g
2.00	2	PEG-400 (low color)	20.00 g
2.00	3	PEG-8000	20.00g
0.25	4	FD&C Red Dye No. 30 lake	2.50 g
2.00	5	Titanium dioxide (special coating grade)	20.00 g
QS	6	Deionized purified water	QS to 1 L

MANUFACTURING DIRECTIONS

Charge 250 ml of water into a suitable container, and heat to 60 to 70°C. With gentle stirring, disperse the hydroxypropyl methyl cellulose onto the hot water; when the cellulose has wetted, quickly add 250 mL of cold water. Stir until the dispersion is homogenous, although the solution of cellulose may not be complete. Dissolve PEG-8000 in 50 ml of water, then add to step above. Add PEG-400 to basic

solution above. Load a suitable size ball jar with the FD&C Red Dye No. 30 and titanium dioxide. Add sufficient water to cover the pigment and balls. Mill overnight or for 12 hours. Other pigment reduction methods may be used to yield a particle size not greater than 1.0 µm. Add milled pigments to the base solution from the step above, and bring the volume up with cold water. Use within 7 days.

B. Cherry Red

Bill of Materials			
Scale (% w/v)	Item	Material Name	Quantity/L
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00 g
2.00	2	PEG-400 (low color)	20.00 g
2.00	3	PEG-8000	20.00 g
1.80	4	FD&C Red Dye No. 3 lake	18.00 g
0.10	5	FD&C Red Dye No. 2 (Amaranth)	1.00 g
2.10	6	Titanium dioxide (special coating grade)	21.00 g
QS	7	Deionized purified water, USP	QS to 1 L

C. Geranium Rose

Bill of Materials			
Scale (% w/v)	Item	Material Name	Quantity/L
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00 g
2.00	2	PEG-400 (low color), NF	20.00 g
2.00	3	PEG-8000	20.00 g
0.24	4	FD&C Red Dye No. 3 lake	2.00 g
QS	5	Deionized purified water, USP	QS to 1 L

D. Gloss

Bill of Materials			
Scale (% w/v)	Item	Material Name	Quantity/L
3.33	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	33.33 g
1.66	2	PEG-400 (low color), NF	16.66 g
QS	3	Deionized purified water, USP	QS to 1 L

E. Red

Bill of Materials			
Scale (% w/v)	Item	Material Name	Quantity/L
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00 g
2.00	2	PEG-400 (low color), NF	20.00 g
2.00	3	PEG-8000	20.00 g
2.50	4	FD&C Red Dye No. 3 lake	25.00 g
0.50	5	Titanium dioxide	5.00 g
QS	6	Deionized purified water, USP	QS to 1 L

F. Moderate Red

Bill of Materials			
Scale (% w/v)	Item	Material Name	Quantity/L
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00 g
2.00	2	PEG-400 (low color), NF	20.00 g
2.00	3	PEG-8000	20.00 g
0.50	4	FD&C Yellow Dye No. 3 aluminum lake	5.00 g
2.50	5	Ponceau Red Dye 4R lake	25.00 g
1.00	6	Titanium dioxide (special coating grade), USP	10.00 g
QS	7	Deionized purified water, USP	QS to 1 L

G. Clear

Bill of Materials			
Scale (% w/v)	Item	Material Name	Quantity/L
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00 g
0.10	2	Sorbic acid	1.00 g
2.00	3	Alcohol (200 proof), SD 3A	20.00 mL
2.00	4	PEG-400 (low color) ^a	20.00 g
2.00	5	PEG-8000 (optional)	20.00 g
QS	6	Deionized purified water	QS to 1 L

^a Increase amount to 6.00 if item 5 is not used.

MANUFACTURING DIRECTIONS

Charge approximately 500 mL of water into a suitable vessel. Heat water to 65 to 70°C. Add the PEG-8000 to the hot water and dissolve (if used). While maintaining gentle agitation, sprinkle the hydroxypropyl methyl cellulose onto the surface of the hot water solution. Position stirring head to avoid excessive entrainment of air. When the cellulose has been dispersed, add the PEG-400. Continue to stir until dispersion is homogeneous, although

solution of cellulose may not be complete. Stop stirring, and allow solution to stand until entrained air is removed. Dissolve sorbic acid in alcohol, and ensure that the solution is complete. When the solution from the step above is clear, add 250 mL of cold water, mix well, and add sorbic acid solution. Mix, then bring up to volume with cold water. Store coating solution in well-filled, well-sealed containers. Use within 3 months.

H. Green

Bill of Materials			
Scale (% w/v)	Item	Material Name	Quantity/L
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00 g
0.10	2	Sorbic acid	1.00 g
2.00 v/v	3	Alcohol (200 proof), SD 3A	20.00 mL
2.00	4	PEG-400 (low color)	20.00 g
2.00	5	PEG-8000	20.00 g
1.00	6	Titanium dioxide (coating grade)	10.00 g
0.01	7	Dye Yellow E104 aluminum lake	0.10 g
0.0032	8	FD&C Blue Dye No. 1 lake (11 – 13%)	0.032 g
QS	9	Deionized purified water	QS to 1 L

I. Holberry Red

Bill of Materials			
Scale (% w/v)	Item	Material Name	Quantity/L
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00 g
0.10	2	Sorbic acid	1.00 g
2.00 v/v	3	Alcohol (200 proof), SD 3A	20.00 mL
2.00	4	PEG-400 (low color)	20.00 g
2.00	5	PEG-8000	20.00 g
1.00	6	Titanium dioxide (coating grade)	10.00 g
1.50	7	FD&C Red Dye No. 40 lake (29%)	15.00 g
0.50	8	FD&C Blue Dye No. 3 lake	5.00 g
QS	9	Deionized purified water	QS to 1 L

J. Sun Orange

Bill of Materials			
Scale (% w/v)	Item	Material Name	Quantity/L
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00 g
0.17	2	Sorbic acid, NF	1.70 g
2.00 v/v	3	Alcohol (200 proof), SD 3A	20.00 mL
2.00	4	PEG-400 (low color), NF	20.00 g
2.00	5	PEG-8000	20.00 g
2.38	6	Titanium dioxide (coating grade), USP	23.80 g
2.47	7	FD&C Yellow Dye No. 5	24.70 g
0.16	8	FD&C Yellow Dye No. 6	1.60 g
QS	9	Deionized purified water, USP	QS to 1 L

K. Opadry Yellow

Bill of Materials			
Scale (mg/caplet)	Item	Material Name	Quantity/1000 Caplets (g)
10.00	1	Hydroxypropyl methyl cellulose (hypromellose)	10.00
4.00	2	Talc (fine powder)	4.00
1.60	3	PEG-4000	1.60
1.20	4	Titanium dioxide	1.20
0.30	5	FD&C Blue Dye No. 1 lake	0.30
0.50	6	FD&C Blue Dye No. 2 (dispersed)	0.50
0.75	7	Opadry-OY-S 29019 (clear)	0.75
QS	8	Purified water	225.00

MANUFACTURING DIRECTIONS

The formula for this coating solution is prepared to obtain a weight gain of 10 mg per caplet (around 600 mg in weight). Disperse item 1 in 175 g of purified water (70 to 80°C) while stirring. Hold overnight for complete dispersion. Disperse items 2 and 3 in 25 g of purified water (25 to 30°C). Hold overnight for complete hydration. Add mixture from previous step. Homogenize using a homogenizer (gap setting, 1.5 mm). Homogenize items 4, 5, and

6 in 50 g of hypromellose dispersion from step above twice, using a homogenizer (gap setting, 1.5 mm). Pass the dispersion twice through a 90-µm sieve. (*Note:* This is a critical step; follow instructions closely to prevent foreign particles and spots.) *Preparation of polishing solution:* Disperse item 7 in 25 g of purified water with slow stirring. Make a vortex by slow stirring and add the powder in such a way as to avoid foam formation.

L. Opadry Yellow

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Hydroxypropyl methyl cellulose (hypromellose)	10.00
4.00	2	Talc (fine powder)	4.00
1.60	3	PEG-4000	1.60
1.34	4	Titanium dioxide	1.34
0.046	5	Sunset Yellow E110, FCF	0.046
1.34	6	FD&C Yellow Dye No. 10 lake	1.34
0.75	7	Opadry-OY-S 29019 (clear)	0.75
QS	8	Purified water	225.00

M. Opadry Red

Bill of Materials			
Scale (mg/caplet)	Item	Material Name	Quantity/1000 Caplets (g)
10.00	1	Hydroxypropyl methyl cellulose (hypromellose)	10.00
4.00	2	Talc (fine powder)	4.00
1.60	3	PEG-4000	1.60
1.34	4	Titanium dioxide	1.34
0.15	5	Iron oxide red	0.15
0.75	6	Opadry-OY-S (clear)	0.75
QS	7	Purified water	225.00

N. Opadry Green

Bill of Materials			
Scale (mg/caplet)	Item	Material Name	Quantity/1000 Caplets(g)
10.00	1	Hydroxypropyl methyl cellulose (hypromellose)	10.00
4.00	2	Talc (fine powder)	4.00
1.60	3	PEG-4000	1.60
2.125	4	Titanium dioxide	2.125
0.053	5	FD&C Blue Dye No. 1 lake	0.053
0.15	6	FD&C Yellow Dye No. 10 lake	0.15
0.75	7	Opadry-OY-S (clear)	0.75
QS	8	Purified water	225.00

MANUFACTURING DIRECTIONS

Disperse item 1 in 175 g of purified water (70 to 80°C) while stirring. Keep overnight for complete dispersion. Disperse items 2 and 3 in 25 g of purified water (25 to 30°C). Keep overnight for complete hydration. Add together and homogenize using homogenizer (gap setting, 1.5 mm). Homogenize items 4, 5, and 6 in 50 g of hypromellose dispersion twice, using homogenizer (gap

setting, 1.5 mm). Pass the dispersion twice through a 90- μ m sieve. (*Note:* This is a critical step; follow instructions closely to prevent foreign particles and spots.) Disperse item 7 in 25 g of purified water while stirring slowly. Make a vortex by slow stirring and add the powder in such a way as to avoid foam formation. Follow the parameters for coating in Accela Cota:

Caplet load	620 g
Pan speed	4 rpm
Drying air temperature	70 – 75°C
Exhaust temperature	50 – 55°C
Fluid pressure	15 – 20 psi
Valve on spray gun	One revolution open
Atomizing pressure	55 psi
Nozzle orifice	1 mm
Nozzle distance to bed	250 – 280 mm
Difference of air pressure	–1.0 to –1.5 cm
Spray rate	200 – 225 g/min
Coating time	3.0 – 3.5 hours

Stir the dispersion at slow speed (6 to 10 rpm) continuously. Spray the polishing solution under the same conditions as above, adjusting the spray rate to 180 g/min. Check the caplet surface every 5 minutes for sticking. If sticking tends to appear, stop the coating immediately. When the spraying is over, roll the tablets in a pan for 10

minutes with cold air blowing onto the caplets. Unload the film-coated caplets into stainless steel containers lined with polyethylene bags. Appearance is a light green, film-coated caplet that is smooth, with no sticking or chipping on the caplet surface. Weight gain per caplet is NLT 10 mg/tablet.

O. White Coating

Bill of Materials			
Scale(mg/tablet)	Item	Material Name	Quantity/1000 Tablets(g)
22.75	1	Hyperomellose	22.75
4.54	2	Polyethylene glycol	4.54
12.50	3	Talc (fine powder)	12.50
10.00	4	Titanium dioxide	10.00
1.30	5	FD&C Yellow No. 10 lake	1.30
—	6	Purified water	~24.00
—	7	Ethanol (95%)	~21.00

III. HYDROXYPROPYL METHYLCELLULOSE OPAQUE ORGANIC COATING

A. Brite Green

Bill of Materials			
Scale(%, w/v)	Item	Material Name	Quantity/L(g)
1.00	1	Titanium dioxide	10.00
50.00 v/v	2	Alcohol (200 proof), SD 3A	~397.00
1.69	3	PEG-400 (low color), NF	16.90
0.02	4	FD&C Yellow Dye No. 5	0.20
0.0068	5	FD&C Blue Dye No. 1	0.068
4.00	6	Hydroxypropyl methyl cellulose 2910 (15 cps)	40.00
QS	7	Methylene chloride	~625.00

MANUFACTURING DIRECTIONS

Charge titanium dioxide and QS with alcohol into a Ball mill. Mill the material for 16 hours. Charge 465 mL alcohol into a suitable mixing tank. Start agitation. Slowly add PEG-400 to mixing tank. Mix for 5 minutes. Add FD&C Yellow Dye to the mixing tank with continued agitation. Rinse bottle with alcohol tapped from mixing tank. Return rinse to mixing tank. Add FD&C Blue Dye to the mixing tank, and rinse. Mix for 2 hours. Tap approximately 10 mL of solution from mixing tank after 1/2, 1, and 1-1/2 hours of mixing. Put solution back into mixing tank. (*Note:* Tapping solution ensures that dye is not tapped into lower valve and/or pipeline.) Rinse the Ball mill with two rinses of 11.6 mL alcohol. Reseal the Ball mill, and allow it to run 2 to 5 minutes between rinses. Empty content of the Ball mill and rinses into mixing tank. Slowly sprinkle hydroxypropyl methyl cellulose into mixing tank with constant agitation. Agitate for an additional 15 minutes. (*Note:* Prevent the

development of lumps by slowly sprinkling hydroxypropyl methyl cellulose into the alcohol.) After mixing 10 minutes, tap approximately 10 mL from the mixing tank and put back into tank to recirculate. Add sufficient methylene chloride (~474 mL) to bring up to volume. Continue agitation for 2 hours. After 1/2, 1, and 1-1/2 hours, tap approximately 10 mL of solution from mixing tank and put back into mixing tank to recirculate. (*Note:* No residue should be present in the solution when tapped at 1-1/2 hours; if some is present, then continue agitation and tap every 15 minutes until no residue is observed.) (*Caution:* Avoid contact with methylene chloride and vapors; they may have toxic effects when swallowed or inhaled.) (*Note:* Nitrogen pressure may be used to assist bottle filling.) Strain mixing tank contents through two-ply cheesecloth, or similar, into suitable approved containers (one half the total number of bottles). (*Note:* Lumps may obstruct spray nozzle.)

B. Red Mahogany

Bill of Materials			
Scale(%, w/v)	Item	Material Name	Quantity/L(g)
0.40	1	Titanium dioxide	4.00
45.00 v/v	2	Alcohol (200 proof), SD 3A	~375.30
0.40	3	Vanillin (crystals)	4.00
1.00	4	Propylene glycol	10.00
1.50	5	FD&C Red Dye No. 40 lake (29%)	15.00
1.00	6	Dye Brown lake blend	10.00
4.00	7	Hydroxypropyl methyl cellulose 2910 (15 cps)	40.00
QS	8	Methylene chloride	~530.40

C. Sun Orange

Bill of Materials			
Scale(%)	Item	Material Name	Quantity/L(g)
3.00 (w/v)	1	Titanium dioxide	30.00
50.00 (v/v)	2	Alcohol (200 proof), SD 3A	~397.00
2.11 (w/v)	3	Propylene glycol	21.10
3.11 (w/v)	4	FD&C Yellow Dye No. 5	31.10
0.20 (w/v)	5	FD&C Yellow Dye No. 6	2.00
4.00 (w/v)	6	Hydroxypropyl methyl cellulose 2910 (15 cps)	40.00
QS	7	Methylene chloride	~625.00

D. Dark Red

Bill of Materials			
Scale(%, w/v)	Item	Material Name	Quantity/L(g)
1.00	1	Titanium dioxide	10.00
20.00 v/v	2	Alcohol (200 proof), SD 3A	~200.00 mL
2.00	3	PEG-400 (low color)	20.00
0.02	4	Ponceau 4R dye (red)	20.00
0.0068	5	FD&C Blue Dye No. 1	0.068
2.95	6	Hydroxypropyl methyl cellulose 2910 (15 cps)	29.50
QS	7	Methylene chloride	QS to 1 L

E. Deep Yellow

Bill of Materials			
Scale(%, w/v)	Item	Material Name	Quantity/L
2.00	1	Titanium dioxide	20.00 g
50.00	2	Alcohol (200 proof), SD 3A	~397.00 g
2.00	3	PEG-400 (low color)	20.00 g
2.00	4	FD&C Yellow Dye No. 5 lake	20.00 g
2.95	5	Hydroxypropyl methyl cellulose 2910 (15 cps)	29.50 g
QS	6	Methylene chloride	QS to 1 L

F. Pale Yellow

Bill of Materials			
Scale(% w/v)	Item	Material Name	Quantity/L
1.50	1	Titanium dioxide	15.00 g
50.00	2	Alcohol (200 proof), SD 3A	~397.00 g
2.00	3	PEG-400 (low color), NF	20.00 g
0.50	4	FD&C Yellow Dye No. 10 aluminum lake (14–17%)	5.00 g
2.95	5	Hydroxypropyl methyl cellulose 2910 (15 cps)	29.50 g
QS	6	Methylene chloride	QS to 1 L

G. Scarlet Red

Bill of Materials			
Scale(% w/v)	Item	Material Name	Quantity/L
2.00	1	Titanium dioxide	20.00 g
20.00	2	Alcohol (200 proof), SD 3A	~200.00 g
2.00	3	PEG-400 (low color), NF	20.00 g
2.00	4	FD&C Yellow Dye No. 7 lake	20.00 g
1.00	5	FD&C Yellow Dye No. 5 lake	10.00 g
2.95	6	Hydroxypropyl methyl cellulose 2910 (15 cps)	29.50 g
QS	7	Methylene chloride	QS to 1 L

IV. HYDROXYPROPYL METHYL CELLULOSE/HYDROXYPROPYL CELLULOSE (KLUCEL®) COATING

A. White

Bill of Materials			
Scale(% w/v)	Item	Material Name	Quantity/L
2.00	1	Titanium dioxide	20.00 g
0.50	2	Hydroxypropyl cellulose, NC	5.00 g
45.00	3	Alcohol (200 proof), SD 3A	~450.00 g
2.00	4	Propylene glycol	20.00 g
4.50	5	Hydroxypropyl methyl cellulose 2910 (15 cps)	45.00 g
QS	6	Methylene chloride	QS to 1 L

MANUFACTURING DIRECTIONS

Place the titanium dioxide and sufficient methylene chloride into suitably sized ball jars to cover the balls. Mill for not less than 16 hours. While mixing the alcohol, add and disperse the hydroxypropyl methyl cellulose, hydroxypropyl cellulose, and propylene glycol, followed by 250 mL of methylene chloride. Continue mixing until the dis-

solution is complete. While mixing the solution from the second step, empty into it the contents of the ball jar, rinse the balls and jar with methylene chloride, add the rinsing to the batch, and mix. Bring the batch up to volume with methylene chloride, and mix well until homogeneous. Strain the batch through muslin into suitable, approved bottles. Seal and store.

V. HYDROXYPROPYL METHYL CELLULOSE/ETHYL CELLULOSE COATING

A. Reddish Orange Opaque

Bill of Materials			
Scale(% w/v)	Item	Material Name	Quantity/L
1.16	1	Titanium dioxide	11.60 g
45.00	2	Alcohol (dehydrated; 200 proof)	~450.00 g
0.20	3	Vanillin (crystals), NF	2.00 g
0.50	4	Albumen powder (white hen egg)	5.00 g
2.00	3	PEG-400 (low color), NF	20.00 g
1.30	4	FD&C Red Dye No. 3	13.00 g
0.05	5	FD&C Red Dye No. 2 (Amaranth), USP	0.50 g
0.20	6	FD&C Yellow Dye No. 6	2.00 g
2.95	5	Hydroxypropyl methyl cellulose 2910, USP (15 cps)	29.50 g
QS	6	Methylene chloride	QS to 1 L

MANUFACTURING DIRECTIONS

Load the vanillin, albumen, titanium dioxide, FD&C Red Dye No. 3, FD&C Red Dye No. 2, and FD&C Yellow Dye No. 6 into a suitable size ball jar. Add sufficient methylene chloride to cover the pigments and balls. Mill for 24 hours. Measure 400 mL of alcohol into a suitable stainless steel container. Sprinkle the hydroxypropyl methyl cellulose/ethyl cellulose onto the surface of the alcohol while stirring vigorously. When the hydroxypro-

pyl methyl cellulose/ethylcellulose has been wetted, quickly add 300 mL methylene chloride while stirring vigorously. Add the PEG-400 to the solution from above, and rinse the container with the remaining alcohol; add the rinsings to the bulk. Empty the contents of the ball jar from the first step into the coating solution from previous step, while stirring vigorously. Rinse the ball jar with methylene chloride; add the rinsings to the bulk. Bring up to volume with methylene chloride.

B. Subcoating Solution

Bill of Materials			
Scale(% w/v)	Item	Material Name	Quantity/L
45.00	1	Alcohol (190 proof), USP	450.00 mL
0.50	2	Hydroxypropyl cellulose, NF	5.00 g
4.50	3	Hydroxypropyl methyl cellulose 2910, USP (15 cps)	45.00 g
QS	4	Methylene chloride	QS to 1 L

VI. HYDROXY METHYL CELLULOSE/HYDROXY CELLULOSE COATING

A. Blue

Bill of Materials			
Scale(% w/v)	Item	Material Name	Quantity/L
1.00	1	Hydroxy methyl cellulose	10.00 g
1.00	2	Hydroxy ethyl cellulose (15 cps)	10.00 g
0.312	3	Titanium dioxide	3.21 g
1.00	4	FD&C Blue Dye No. 1 lake (12%)	10.00 g
0.375	5	Castor oil (odorless)	3.75 g
0.375	6	Sorbitan monooleate	3.75 g
50.00	7	Alcohol (200 proof), SD 3A	500.00 mL
QS	8	Methylene chloride	QS to 1 L

MANUFACTURING DIRECTIONS

Premix hydroxypropyl methyl cellulose and hydroxypropyl cellulose, and add to 440 mL alcohol with rapid agitation. Mix for not less than 1 hour. Charge FD&C Blue Dye and titanium dioxide into a ball mill. Cover the balls and materials with 60 mL of alcohol, and mill for 16 hours.

Add contents to mixing tank, and add the castor oil and sorbitan monooleate. Rinse the ball mill with methylene chloride, and add the rinsings to the mixing tank. Bring up to a volume of 1 L with methylene chloride, and mix for at least 1 hour.

B. Clear (50:50)

Bill of Materials			
Scale(% w/v)	Item	Material Name	Quantity/L
1.00	1	Hydroxy methyl cellulose	10.00 g
1.00	2	Hydroxy ethyl cellulose, USP (15 cps)	10.00 g
0.375	3	Castor oil (odorless)	3.75 g
50.00	4	Alcohol (200 proof), SD 3A	500.00 mL
QS	5	Methylene chloride	QS to 1 L

VII. HYDROXY METHYL CELLULOSE/ETHYL CELLULOSE COATING

A. Clear

Bill of Materials			
Scale(% w/v)	Item	Material Name	Quantity/L
1.00	1	Hydroxy methyl cellulose	10.00
1.00	2	Hydroxy ethyl cellulose, USP (15 cps)	10.00
0.375	3	Castor oil (odorless), USP	3.75
50.00	4	Alcohol (200 proof), SD 3A	500.00 mL
QS	5	Methylene chloride	QS to 1 L

MANUFACTURING DIRECTIONS

Charge all the alcohol into mixing tank. Turn on mixer to mixing speed; maintain mixing speed throughout preparation of coating solution. Charge the hydroxypropyl methyl cellulose and ethyl cellulose into the mixing tank.

Let mix for 1 hour. Add methylene chloride (~500 mL) to bring the final volume up to 1 L. Mix 1 hour. Solution need not be agitated at all times. Keep tank tightly closed at all times. Rubber stopper on bottles must be protected from methylene chloride with a polyethylene layer.

VIII. POLYVINYLPIRROLIDONE (PVP) COATINGS

A. Subcoating

Bill of Materials			
Scale(% w/v)	Item	Material Name	Quantity/L
20.00	1	Povidone USP K-29-32 ^a	200.00 g
80.00	2	Alcohol (200 proof), SD 3A	800 mL

^a May be substituted with Kollidon® VA 64 (polyvinylpyrrolidone/vinylacetate copolymer; 10%), and item 2 can be replaced with isopropyl alcohol.

MANUFACTURING DIRECTIONS

Spray the solution onto the warm tablet cores (30 to 40°C) for a few minutes before continuing with the main aqueous coating procedure. The amount of 0.4 mg/cm² tablet sur-

face is sufficient for good subcoating protection. No plasticizer is needed in this formulation due to the plasticity of Kollidon VA 64.

B. Kollidon® VA 64 (Polyvinylpyrrolidone/Vinylacetate Copolymer, BASF)

Bill of Materials			
Scale(%, w/w)	Item	Material Name	Quantity/kg
5.00	1	Kollidon® VA 64	50.00 g
4.00	2	Lutrol E 6000	40.00 g
0.50	3	Glycerin, USP	5.00 g
1.50	4	Iron oxide or lake	15.00 g
3.00	5	Titanium dioxide	30.00 g
5.00	6	Talc	50.00 g
QS	7	Purified water	QS to 1 L

MANUFACTURING DIRECTIONS

Pass the suspension through a disk mill prior to use and spray under the following conditions:

Sugar-Coating Pan

Spray gun	Walther WAXV with 1-mm nozzle
Spraying time	3 seconds
Pause	0.5 seconds
Dry air	6 seconds
Pause	3 seconds

Accela Cota (Continuous Spraying)

Spray gun	Walther WAXV with 0.8-mm nozzle
Temperature at inlet	45°C
Temperature at outlet	38°C
Spraying pressure	2 bar
Spraying time	~50 minutes

If the film is too sticky, a certain part of the Kollidon should be substituted by HPMC or sucrose.

C. Kollidon® VA 64 and Polyvinyl Alcohol

Bill of Materials			
Scale(%, w/w)	Item	Material Name	Quantity/kg
5.0	1	Kollidon® VA 64	50.00 g
4.00	2	Lutrol E 6000	40.00 g
6.00	3	Polyvinyl alcohol	76.00 g
68.00	4	Purified water	680.00 g
0.50	5	Glycerin, USP	5.00 g
1.50	6	Iron oxide or lake	18.00 g
3.00	7	Titanium dioxide	37.00 g
5.00	8	Talc	50.00 g
QS	9	Purified water	168.00 g

MANUFACTURING DIRECTIONS

Dissolve items 1 to 3 in item 4, add the polyvinyl alcohol, and stir 45 minutes, avoiding the formation of too many air bubbles. Suspend the pigments and talc in 168 mL of

water, and pass this mixture through a colloid mill. To obtain the final coating suspension, mix this solution with the first solution. Suggested conditions for coating using Accela-Cota are given below.

Tablet core loading	5.0 kg
Amount of coating suspension	1.26 kg
Inlet air temperature	59°C
Outlet air temperature	46°C
Nozzle	1.0 mm
Rotation speed of the pan	15 rpm
Spraying pressure	2.0 bar
Spraying rate	15 g/minute
Spraying time (continuously)	83 minutes
Final drying	5 minutes
Quantity of film former applied	~3 mg/cm ²

D. Kollidon® 30 and Shellac

Bill of Materials			
Scale (%, w/w)	Item	Material Name	Quantity/kg(g)
2.00	1	Kollidon® 25 or 30	20.00
17.70	2	Shellac	177.00
18.50	3	Titanium dioxide	185.00
6.50	4	Talc	65.00
1.50	5	Cetyl alcohol	15.00
3.00	6	Sorbitan trioleate	30.00
5.00	7	Color lake	50.00
QS	8	Isopropanol or alcohol	458.00

MANUFACTURING DIRECTIONS

Dissolve shellac and sorbitane trioleate in the warm solvent and then the Kollidon and cetyl alcohol. Add titanium dioxide, talc, and the lake, and mix in the colloid mill.

Application of the coating suspension: About 50 g of suspension is applied to 1 kg of tablet cores in a conventional coating pan or in an Accela-Cota pan (1 to 2 mg film formers/cm²).

E. Kollidon® VA 64 and Hydroxypropyl Methyl Cellulose

Bill of Materials			
Scale(%, w/w)	Item	Material Name	Quantity/kg
4.00	1	Kollidon® VA 64	53.00 g
1.00	2	Lutrol E 6000	12.00 g
6.00	3	Hydroxypropyl methyl cellulose	79.00 g
1.50	4	Iron oxide or lake	18.00 g
3.00	5	Titanium dioxide	37.00 g
4.00	6	Talc	50.00 g
QS	7	Purified water	QS to 1 kg

MANUFACTURING DIRECTIONS

Dissolve Lutrol and Kollidon in a portion of the water, add hydroxypropyl methyl cellulose, and stir 45 minutes, avoiding the formation of too many air bubbles. Suspend

the pigments and talc in a portion of the water, and pass this mixture through a colloid mill. Mix the two portions. Conditions for coating using Acela-Cota are given below.

Tablet core loading	5.0 kg
Core size	9-mm biconvex
Amount of coating suspension applied	1.2 kg
Inlet air temperature	60°C
Outlet air temperature	40°C
Nozzle	1.0 mm
Rotation speed of the pan	12 rpm
Spraying pressure	2.0 bar
Spraying rate	50 g/minute
Spraying time (continuously)	34 minutes
Final drying	2 minutes
Drying after spraying	5 minutes at 60°C
Quantity of film-former applied	3.14 mg/cm ²

F. Povidone, Ethyl Cellulose, and Talc

Bill of Materials			
Scale(%, w/v)	Item	Material Name	Quantity/L
7.50	1	Povidone (PVP K-29–32), USP	75.00 g
4.25	2	Ethyl cellulose, NF	42.50 g
0.50	3	PEG-400, NF	5.00 g
5.00	4	Talc	50.00 g
45.00	5	Alcohol (200 proof), SD 3A	450.00 mL
QS	6	Methylene chloride, NF	QS to 1 L

MANUFACTURING DIRECTIONS

Dissolve Povidone in alcohol and then add PEG-400. Add ethyl cellulose to this solution. Mix until evenly dispersed, then bring up to volume with methylene chloride with constant stirring. Add the talc to this solution, and stir to

ensure distribution. Solution should be freshly prepared and used within 10 days of manufacture. Thoroughly disperse talc before use. If batch is more than 200 L, do not add talc. If coating solution is manufactured without talc, then solution should be used within 4 weeks.

IX. CELLULOSE ACETATE PHTHALATE AND CARBOWAX COATINGS

A. Brite Green

Bill of Materials			
Scale(% w/v)	Item	Material Name	Quantity/L
6.00	1	Cellulose acetate phthalate (carbowax)	60.00 g
1.86	2	Propylene glycol	18.65 g
0.66	3	Sorbitan monooleate (Span 80)	6.00 g
0.12	4	Castor oil (odorless)	1.25 g
0.85	5	FD&C Blue Dye No.1	0.85 g
3.11	6	FD&C Yellow Dye No. 5 lake	31.10 g
5.33	7	Titanium dioxide	53.30 g
21.58	8	Methylene chloride	215.00 g
QS	9	Acetone	QS to 1 L

MANUFACTURING DIRECTIONS

Place the methylene chloride in a suitably sized mixing tank. While stirring, add the propylene glycol, Span 80, and castor oil. To this mixture add the cellulose acetate phthalate, and allow to soak overnight. Load the dyes and titanium dioxide into a suitable ball jar. Add sufficient acetone to cover the raw materials and balls. Ball mill overnight. Melt the Carbowax with a portion of the acetone using gentle heat. Add the melted Carbowax to the mixture from the second step. Empty contents of ball jar mill to this mixture. Rinse the ball jar with acetone, and add rinsings. Add acetone to volumem and mix well. If necessary, strain solution through gauge before storage or use.

B. Cherry Red

In the formulation given above, use, FD&C Red Dye No. 3 (6.800 g), FD&C Red Dye No. 2 (Amaranth, USP; 1.00 g), and FD&C Yellow Dye (5.40 g).

C. Clear

Delete dyes.

D. Orange

Use FD&C Yellow Dye No. 6 (4.00 g) and FD&C Yellow Dye No. 5 (12.00 g).

X. SUGAR COATINGS

A. Basic

Bill of Materials			
Scale(%, w/w)	Item	Material Name	Quantity/kg
4.00	1	Kollidon® VA 64	40.00 g
16.00	2	Sucrose	160.00 g
2.40	3	Titanium dioxide	24.00 g
1.20	4	Color lake	12.00 g
3.20	5	Lutrol E 4000	32.00 g
4.00	6	Talc	40.00 g
QS	7	Purified water	QS to 1 kg

MANUFACTURING DIRECTIONS

Dissolve the sucrose, Kollidon, and Lutrol in the water, and suspend the other components. Pass through a colloid mill. Use the following conditions for use in Accela-Cota.

Tablet core loading	5.00 kg
Amount of coating suspension	1.20 kg
Inlet air temperature	45°C
Outlet air temperature	35°C
Nozzle	0.80 mm
Rotation speed of the pan	15 rpm
Spraying pressure	2.0 bar
Spraying time (continuously)	50 minutes
Quantity of film-former applied	4.00 mg/cm ²

B. Automatic

Bill of Materials			
Scale(%, w/w)	Item	Material Name	Quantity, g/Kg
4.00	1	Kollidon® 30	40.00
38.00	2	Sucrose	380.00
4.50	3	Titanium dioxide	45.00
QS	4	Color lake	QS
4.50	5	Calcium carbonate	45.00
14.50	6	Talc	145.00
QS	7	Purified water	QS to 1 kg

MANUFACTURING DIRECTIONS

Dissolve the sucrose in the hot water, then mix with glycerol. Dissolve Kollidon and suspend the other components.

Coating Procedure

Coat 4 kg of tablet cores with a weight of 420 mg each by spraying with 2.5 kg of the above suspension in a conventional coating pan under the following conditions:

Spray phase	5 seconds
Interval	10 minutes
Drying phase (warm air)	10 minutes
Total coating time	16 hours

C. Manual, White

Bill of Materials			
Scale(%, w/w)	Item	Material Name	Quantity/kg(g)
0.33	1	Kollidon® 30	3.36
0.29	2	Carmellose sodium	2.92
0.21	3	Aerosil® 200	2.14
QS	4	Color lake (white)	QS
1.62	5	Talc	16.20
0.10	6	Polysorbate or Cremophor RH40	1.00
1.40	7	Titanium dioxide	14.00
62.70	8	Sucrose	627.00
33.40	9	Purified water	334.00

MANUFACTURING DIRECTIONS

Dissolve Kollidon, polysorbate or Cremophor and sucrose in the water, and suspend the other components in this solution. Mix in a colloid mill. Start with formulation

without the color and then apply the color coat. The polishing can be done by means of a solution of beeswax or PEG-6000.

XI. ENTERIC COATINGS

A. Kollicoat® and Kollidon® Enteric Film Coating

Bill of Materials			
Scale(% w/w)	Item	Material Name	Quantity/kg
0.50	1	Titanium dioxide	5.00 g
2.00	2	Talc	20.00 g
0.50	3	Iron oxide	5.00 g
0.50	4	Kollidon® 25 or Kollidon® 30	5.00 g
50.00	5	Kollicoat® MAE 30 DP (methacrylic acid/ethyl acrylate copolymer, 1:1)	500.00 g
1.50	6	Triethyl citrate	15.00 g
QS	7	Purified water	QS to 1 kg

MANUFACTURING DIRECTIONS/CONDITIONS

Tablet core loading	5 kg
Core size	9-mm biconvex
Quantity of suspension applied	1890 g
Quantity of solids/cm ²	9 mg
Quantity of film-forming agent/cm ²	6 mg
Speed of the coating pan	12 rpm
Spray nozzle	0.8 mm
Spraying pressure	2.0 bar
Type of spraying	Continuous
Inlet air temperature	50°C
Outlet air temperature	~30°C
Spraying time	~60 minutes
Spraying rate	~30 g/minutes

XII. EUDRAGIT® ENTERIC AQUEOUS

A. Brick Red

Bill of Materials			
Scale(% w/w)	Item	Material Name	Quantity/kg (g)
46.667	1	Distilled purified water	466.667
1.519	2	Talc (powder)	15.198
0.798	3	Titanium dioxide (special coating grade)	7.983
1.55	4	Iron oxide, red	15.50
0.426	5	Polysorbate 80	4.262
0.015	6	Dimethyl polysiloxane emulsion (30%)	0.155
47.60	7	Eudragit®; use Eudragit® L 30D-55	476.00
1.426	8	Triethyl citrate (Eudraflex®)	14.259

MANUFACTURING DIRECTIONS

Weigh the quantity of water needed. Put approximately 21.5% of the total quantity of water in a suitable mixing container. Add the talc powder, and stir vigorously until well suspended (approximately 20 minutes). Add the following to this suspension, and mix thoroughly: titanium dioxide, iron oxide, Tween 80, dimethyl polysiloxane emulsion (30%). (*Note:* The pigments may require

homogenizing with colloid, corundum disc mill, or ball mill.) Put the Eudragit in a suitable mixing vessel, and add the following with continuous mixing: homogenized pigment mixture, Eudraflex (i.e., triethyl citrate), and remaining quantity of water. (*Note:* When PEG-8000 is used as a plastisizer, it should be incorporated as a 10% aqueous solution.)

B. Yellow

Bill of Materials			
Scale(% w/w)	Item	Material Name	Quantity/kg(g)
46.66	1	Distilled purified water	466.66
1.25	2	Talc (powder)	12.57
0.77	3	Titanium dioxide (special coating grade)	7.79
1.83	4	FD&C Yellow Dye No. 10 aluminum lake (14 to 17%)	18.36
0.42	5	Polysorbate 80	4.27
0.01	6	Dimethyl polysiloxane emulsion (30%)	0.12
47.6	7	Eudragit®; use methacrylic acid copolymer, NF (Eudragit® L 30D-55)	476.00
1.42	8	Triethyl citrate (Eudraflex®)	14.21

C. Brown

Bill of Materials			
Scale(% w/w)	Item	Material Name	Quantity/kg(g)
46.66	1	Distilled purified water	466.66
0.47	2	Titanium dioxide (special grade coating), USP	4.76
0.85	3	Iron oxide, black	8.53
2.26	4	Iron oxide, red	22.61
0.25	5	Iron oxide, yellow	2.57
0.42	6	Polysorbate 80	4.26
0.01	7	Dimethyl polysiloxane emulsion	0.09
47.63	8	Eudragit®; use Eudragit® L 30D-55	476.33
1.42	9	Triethyl citrate (Eudraflex®)	14.28

D. Dark Orange

Bill of Materials			
Scale(%, w/w)	Item	Material Name	Quantity/kg(g)
46.66	1	Distilled purified water	466.66
2.51	2	Talc (powder)	25.18
0.39	3	Titanium dioxide (special coating grade)	3.92
0.93	4	FD&C Yellow Dye No. 6 aluminum lake	9.32
0.42	5	Polysorbate 80	4.29
0.01	6	Dimethyl polysiloxane emulsion (30%)	0.13
47.63	7	Eudragit®; use Eudragit® L 30D-55	476.33
1.42	8	Triethyl citrate (Eudraflex®)	14.28

E. Orange

Bill of Materials			
Scale(%, w/w)	Item	Material Name	Quantity/kg(g)
46.66	1	Distilled purified water	466.66
2.60	2	Talc (powder)	26.00
0.78	3	Titanium dioxide (special coating grade)	7.84
0.46	4	FD&C Yellow Dye No. 6 aluminum lake	4.66
0.42	5	Polysorbate 80	4.27
0.01	6	Dimethyl polysiloxane emulsion (30%)	0.11
47.61	7	Eudragit®; use Eudragit® L 30D-55	476.16
1.42	8	Triethyl citrate (Eudraflex®)	14.29

F. Dispersed Orange

Bill of Materials			
Scale(mg/tablet)	Item	Material Name	Quantity/1000 Tablets(g)
0.92	1	Opagloss NA 7150	0.92
7.07	2	Methacrylic acid copolymer (Eudragit® L 100-55)	7.07
0.09	3	Sodium hydroxide pellets (caustic soda)	0.09
0.73	4	PEG-6000	0.73
2.50	5	Talc (fine powder)	2.50
0.10	6	Simethicone emulsion 30% (simethicone antifoam M30)	0.10
0.27	7	Povidone (PVP K-25)	0.27
50.00	8	Sucrose	50.00
0.54	9	Povidone (PVP K-25)	0.54
0.36	10	Titanium dioxide	0.36
0.36	11	FD&C Yellow Dye No. 10 lake	0.36
0.04	12	Dispersed orange ^a	0.04
1.07	13	Sucrose	1.07
0.38	14	Polishing emulsion	0.38
—	15	Purified water	65.41

^a Dispersed orange: This material is the aluminum lake of Sunset Yellow FCF (E110).

XIII. HYDROXYPROPYL METHYL CELLULOSE PHTHALATE ENTERIC COATING

A. Clear Enteric

Bill of Materials			
Scale(%)	Item	Material Name	Quantity/kg
20.00 (v/v)	1	Acetone	200.00 mL
10.00 (v/v)	2	Purified Water	100.00 mL
4.00 (w/v)	3	Hydroxypropyl methyl cellulose	40.00 g
0.30 (w/v)	4	Vanillin (crystals)	3.00 g
0.40 (w/v)	5	Acetylated monoglycerides	4.00 g
QS	6	Alcohol (200 proof), SD 3A	QS to 1 L

MANUFACTURING DIRECTIONS

Charge acetone, purified water, and 470 mL of alcohol into a suitable mixing tank. Add the hydroxypropyl methyl cellulose phthalate, vanillin crystals (if used), and the dis-

tilled acetylated monoglycerides. Mix until a clear solution is obtained. Bring up to 1 L with alcohol, and record volume used. Mix for 1 hour.

B. Orchid Pink Opaque

Bill of Materials			
Scale(%)	Item	Material Name	Quantity/kg
20.00 (v/v)	1	Acetone	200.00 mL
10.00 (v/v)	2	Purified water	100.00 mL
8.00 (w/v)	3	Hydroxypropyl methylcellulose phthalate	80.00 g
0.80 (w/v)	4	Diacetylated monoglycerides	8.00 g
0.06 (w/v)	5	Dye Red D&C No. 30 Lake	0.60 g
0.006 (w/v)	6	FD&C Blue Dye No. 2 aluminum lake (14%)	0.06 g
0.70 (w/v)	7	Titanium dioxide	7.00 g
QS	8	Alcohol (200 proof), SD 3A	1

C. Light Apricot Orange

Bill of Materials			
Scale(%, w/v)	Item	Material Name	Quantity/kg
20.00 (v/v)	1	Acetone	200.00 mL
10.00 (v/v)	2	Purified water	100.00 mL
8.00	3	Hydroxypropyl methyl cellulose phthalate	80.00 g
0.80	4	Diacetylated monoglycerides	8.00 g
0.10	5	FD&C Yellow Dye No. 10 aluminum lake (14–17%)	1.00 g
0.06	6	FD&C Red Dye No. 3 aluminum lake (14%)	0.60 g
0.70	7	Titanium dioxide	7.00 g
QS	8	Alcohol (200 proof), SD 3A	To 1 kg

Part I

Regulatory Guidance

1 Good Manufacturing Practices in Over-the-Counter Drug Product Manufacturing

I. INTRODUCTION

All drugs must be manufactured in accordance with current good manufacturing practice regulations; otherwise, they are considered to be adulterated within the meaning of the Federal Food, Drug, and Cosmetic (FD&C) Act, Section 501(a)(2)(B). For an over-the-counter (OTC) drug that is covered by a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA), the U.S. Food and Drug Administration (FDA) may review, copy, and verify the records under Section 505(k)(2) of the FD&C Act. However, if the product is an OTC drug for which no application has been filed with the FDA, a firm is not legally required to show these records to the investigator during an inspection being conducted under Section 704 of the FD&C Act. Nonetheless, all manufacturers of prescription and OTC drugs must comply with the Current Good Manufacturing Practice Regulations (cGMPs) for the drug, including those involving records. On rare occasions, a firm may refuse to allow review of OTC drug records, stating that they are not legally required to do so. While a firm may be under no legal obligation to permit review of such records, this does not relieve the firm of its statutory requirement to comply with the good manufacturing practices under Section 501(a)(2)(B) of the FD&C Act, including the requirements for Organization and Personnel (21 CFR 211, Subpart B).

The firm must have a quality control department that has the responsibility and authority described in the referenced CFR. The quality control department must maintain its independence from the production department, and its responsibilities must be in writing. In the drug industry, the employees' education and training for their positions have a significant impact on the production of a quality product. The training received by employees should be documented. The quality control department must perform annual product reviews on each drug manufactured and must have written annual review procedures. The review report should provide a summary of all lots that failed in-process or finished product testing and other critical factors. The quality control department must validate the manufacturing process for each drug manufactured.

II. BUILDINGS AND FACILITIES (21 CFR 211, SUBPART C)

The construction, size, and location of a plant in relation to its surroundings are important considerations. Adequate lighting, ventilation, screening, and proper physical barriers must be available for all operations, and dust, temperature, humidity, and bacteriological controls must be in place. Adequate blueprints should be available that describe such systems as high-purity water, high-efficiency particulate air (HEPA), and compressed air. Also, the plant must have adequate locker, toilet, and handwashing facilities. The firm must provide adequate space for the placement of equipment and materials to prevent mix-ups in the following operations:

- Receiving, sampling, and storage of raw materials
- Manufacturing or processing
- Packaging and labeling
- Storage for containers, packaging materials, labeling, and finished products
- Production and control laboratories

III. EQUIPMENT (21 CFR 211, SUBPART D)

The design, capacity, construction, and location of equipment used in the manufacturing, processing, packaging, labeling, and laboratories must be properly documented. New equipment must be properly installed and operated as designed. Often, an equipment change requires FDA preapproval and/or revalidation of the manufacturing process. The equipment must be cleaned before use according to written procedures, and the cleaning must be documented and validated. The equipment should not adversely affect the identity, strength, quality, or purity of the drug. The material used to manufacture the equipment must not react with the drug. Also, lubricants or coolants must not contaminate the drug. The equipment should be constructed and located to ease cleaning, adjustments, and maintenance. Also, it should prevent contamination from other or previous manufacturing operations. Equipment

must be identified as to its cleaning status and content. The cleaning and maintenance of the equipment are usually documented in a logbook maintained in the immediate area. The equipment used should be of suitable capacity and accuracy for use in measuring, weighing, or mixing operations. If the equipment requires calibration, a written procedure must be in place for performing and documenting the calibration.

IV. COMPONENTS AND PRODUCT CONTAINERS (21 CFR 211, SUBPART E)

How components, drug product containers, and closures are received, identified, stored, handled, sampled, tested, and approved or rejected must be documented; written procedures must be in place that describe how these operations are carried out. The system must be reviewed to decide if it is functioning correctly. If the handling and storage of components are computer controlled, the program must be validated. (Recently, the FDA has undertaken greater scrutiny of computer validation. It is not required to use computers to handle such data, but where computer systems are not yet validated, alternative parallel systems should be available to corroborate the data validation.)

The receiving records must provide traceability to the component manufacturer and supplier. The receiving records for components should contain the name of the component, manufacturer, supplier (if different from the manufacturer), and carrier. In addition, the records should include the receiving date, manufacturer's lot number, quantity received, and control number assigned by the firm.

The sanitary conditions in the storage area, stock rotation practices, retest dates, and special storage conditions (protection from light, moisture, temperature, air, etc.) must meet the recordkeeping requirements. Glandular and botanical components are subject to insect infestation, and care must be exercised in how these components are stored. Components or finished products adulterated by rodents, insects, or chemicals must be documented, and these can be seized during a regulatory inspection. A firm should keep recorded evidence regarding whether or not it plans to voluntarily destroy such product. Components, colors, and food additives that may be new drug substances, that appear to have no use in the plant, or that seem to be from an unknown supplier may not be stored along with other in-use components and ingredients. Any colors should be checked against the Color Additives Status List in the Investigation Operations Manual of the FDA (IOM) to ascertain if they are approved for their intended use and that the required statements are declared on the drug labels.

When components are received at more than one location, they must be handled in accordance with the drug

cGMPs, including components used in research and development laboratories. Components must be identified so the status (quarantine, approved, or rejected) is known. The criteria for removing components from quarantine should be properly established, along with criteria for the movement of components to other areas and the handling of rejected components. The component container should have an identification code affixed to it. This unique code provides traceability from the component manufacturer to its use in the finished product. The sampling and testing procedures for components and the process by which approved materials are released for use should be adequate and available for inspection. The validity and accuracy of a firm's inventory system for drug components, containers, closures, and labeling should be frequently verified by weighing a lot and comparing the results against the quantity remaining on the inventory record. Significant discrepancies in these records should be investigated.

The following should be evaluated by firms to ensure that containers and closures are compatible with the product, will provide adequate protection for the drug against deterioration or contamination, are not additive or absorptive, and are suitable for use:

- Specifications for containers, closures, cotton filler, and desiccant, etc.
- What tests or checks are made (cracks, glass particles, durability of material, metal particles in ointment tubes, compliance with compendium specifications, etc.)
- Cleaning procedures and how containers are stored
- Handling of preprinted containers (e.g., controlled as labeling or as containers); labeling must be reviewed for accuracy

V. PRODUCTION AND PROCESS CONTROLS (21 CFR 211, SUBPART F)

A. CRITICAL MANUFACTURING STEPS (21 CFR 211.101)

Each critical step in the manufacturing process should be done by a responsible individual and checked by a second responsible individual. If such steps in the processing are controlled by automatic mechanical or electronic equipment, its performance should be verified. Critical manufacturing steps include selection, weighing, measuring, and identifying components, as well as the addition of components during processing. Also critical is the recording of deviations from the batch record, mixing time, testing of in-process material, and determination of actual yield and percent of theoretical yield. These manufacturing steps are documented when done, not before or after the fact.

B. EQUIPMENT IDENTIFICATION

(21 CFR 211.105)

All containers and equipment used to manufacture a drug should be labeled at all times. The label should identify the contents of the container or equipment, including the batch number and stage of processing. Previous identification labels should be removed. The batch should be handled and stored to prevent mix-ups or contamination.

C. IN-LINE AND BULK TESTING

(21 CFR 211.110)

To ensure the uniformity and integrity of products, adequate in-process controls should be in place, such as checking the weights and disintegration times of tablets, the fill of liquids, the adequacy of mixing, the homogeneity of suspensions, and the clarity of solutions. The in-process test equipment should be on site and the specified tests performed as indicated. Prerecording of test results, such as tablet weight determinations, can often reflect a personnel problem and should be strictly discouraged. The bulk drug is usually held in quarantine and not released to the packaging and labeling department until all tests are completed; however, the testing might be done after packaging the product.

D. ACTUAL YIELD (21 CFR 211.103)

Personnel must check actual against theoretical yields of each batch of drug manufactured. In the event of any significant unexplained discrepancies, a procedure must be in place to prevent distribution of the batch in question and related batches.

E. PERSONNEL HABITS

The work habits of plant personnel that are of importance include:

- Attitude and actions involving the jobs they perform (e.g., careless, lackadaisical, disgruntled)
- Attire (e.g., clean dresses, coats, shirts, pants, head coverings)
- Proper use of equipment vs. taking short cuts for a given job (e.g., use of hands and arms to mix or empty trays of drug components)
- Significant written or verbal language barriers that could affect job performance

F. TABLET AND CAPSULE PRODUCTS

The equipment may include rotary tableting machines, coating and polishing pans, punches and dies, etc. The equipment should be constructed and located to facilitate

maintenance and cleaning at the end of each batch or at suitable intervals in the case of a continuous-batch operation. If possible, the cleaning should be observed to determine if cleaning procedures are being followed.

The ingredients in a tablet are the active ingredient, binders, disintegrators, bases, and lubricants. The binder is added to the batch to keep the tablet together. Excess binder will make the tablet too hard for use. The disintegrator is used to facilitate disintegration of the tablet after administration. The base should be an inert substance that is compatible with the active ingredient and is added to provide size and weight. The lubricant aids the flow of granulated material, prevents adhesion of the tablet material to the surface of punches and dies, and facilitates tablet ejection from the machine.

Tablets and capsules are susceptible to airborne contamination because of the manipulation of large quantities of dry ingredients. To prevent cross-contamination in the tableting department, close attention must be paid to the maintenance, cleaning, and location of equipment and the storage of granulations and tablets. To prevent cross-contamination, the mixing, granulation, drying, and/or tableting operations should be segregated in enclosed areas with their own air-handling systems. Document what precautions are being taken to prevent cross-contamination. When cross-contamination is suspect, investigate the problem and collect in-line samples and official samples of the suspect product. Establish what temperature, humidity, and dust-collecting controls are used by the firm in its manufacturing operations. Lack of temperature and humidity controls can affect the quality of the tablet.

Record that powders or granulations are processed according to the standard operating procedures (SOPs). The mixing process must be validated. The drying ovens should have their own air-handling systems to prevent cross-contamination. Firms should maintain charts of drying times and temperatures and should include loss-on-drying test results. Records regarding the disposition of in-process samples should also be maintained.

Capsules may be either hard or soft. They are filled with powder, beads, or liquid by machine. The manufacturing operations for powders for capsules should follow the same practices as for tablets. Manufacturing controls, in-line testing, and bases for evaluating test results for the filling operations should be established.

G. STERILE PRODUCTS

Typically, a sterile drug contains no viable microorganisms and is nonpyrogenic. Drugs for ophthalmic preparations and for administration to other body cavities may be classified as OTC. In addition, other dosage forms might be labeled as sterile — for example, an ointment applied to a puncture wound or skin abrasion. Details of compliance requirements are given in Volume 6 of this series,

Sterile Products. Establish procedures to minimize the contamination of sterile drugs with microorganisms and particulates.

1. Personnel

Establish a training program to ensure that personnel performing production and control procedures have experience and training commensurate with their intended duties. It is important that personnel be trained in aseptic procedures. The employees must be properly gowned and use good aseptic techniques.

2. Buildings

The nonsterile preparation areas for sterile drugs should be controlled — refer to Subpart C of the proposed cGMPs for large-volume parenteral (LVP) drugs; however, deviations from these proposed regulations are not necessarily deviations from the cGMPs. Evaluate the air cleanliness classification of the area. For guidance in this area, review Federal Standard #209E entitled *Airborne Particulate Cleanliness Classes in Cleanrooms and Clean Zones*. Establish formulation practices or procedures to be used in the preparation areas to avert contamination. Minimize traffic and unnecessary activity in the preparation area. Determine how filling rooms and other aseptic areas are to be constructed to eliminate possible areas for microbiological or particulate contamination — for example, minimize dust-collecting ledges, porous surfaces, etc. Establish how aseptic areas are to be cleaned and maintained.

3. Air

Air supplied to the nonsterile preparation or formulation area for manufacturing solutions prior to sterilization should be filtered as necessary to control particulates. Air being supplied to product exposure areas where sterile drugs are processed and handled should be HEPA filtered under positive pressure. A system should be in place for maintaining HEPA filters, including recording whether or not they are certified and/or dioctyl phthalate (DOP) tested, as well as the frequency of testing. The compressed-air system should be filtered at the point of use to control particulates. Diagrams of the HEPA-filter and compressed-air systems should be available.

4. Environmental Controls

Specifications for viable and nonviable particulates must be established. Specifications for viable particulates must include provisions for both air and surface sampling of aseptic processing areas and equipment, the results of which are appropriately recorded. A procedure for reviewing out-of-limit test results should be established. The

environmental test data should be included as a part of the firm's release procedures. *Note:* In the preparation of media for environmental air and surface sampling, suitable inactivating agents should be added — for example, the addition of penicillinase to media used for monitoring sterile penicillin operations and cephalosporin products.

5. Equipment

Establish procedures for how the equipment is to be operated, cleaned, and maintained, as well as procedures for how equipment used in the filling room is to be sterilized, how the sterilization cycle is to be validated, and how the equipment should be resterilized if sterility has been compromised. Catalog the types of filters used, along with the purpose of the filters and how they are assembled, cleaned, and inspected for damage. Methods for microbial retentive filter integrity testing are required.

6. Water for Injection

Water used in the production of sterile drugs must be controlled to assure that it meets U.S. Pharmacopeia (USP) specifications. Have in place a well-established system that includes specifications for water used for the injection, production, storage, and delivery systems. Ensure that the stills, filters, storage tanks, and pipes are installed and operated in a manner that will not contaminate the water. Establish procedures and specifications to maintain the quality of water used for injection.

7. Containers and Closures

Establish procedures for how containers and closures are handled and stored. Ensure that cleaning, sterilization, and depyrogenization procedures are adequate and have been validated.

H. STERILIZATION

1. Methods

Establish clearly the methods used for sterilization. A good source of reference material on validation of various sterilization processes is the *Parenteral Drug Association Technical Reports*; for example, Technical Report #1 covers validation of steam sterilization cycles. Review and evaluate the validation data whatever the method employed. Volume 6 of the *Handbook of Pharmaceutical Manufacturing Formulations* includes additional details.

If steam under pressure is used, an essential control is a mercury thermometer and a recording thermometer installed in the exhaust line. The time required to heat the center of the largest container to the desired temperature must be known. Steam must expel all air from the sterilizer chamber to eliminate cold spots. The drain lines should

be connected to the sewer by means of an air break to prevent back siphoning. The use of paper layers or liners and other practices that might block the flow of steam should be avoided. Charts of time, temperature, and pressure should be filed for each sterilizer load.

If sterile filtration is used, establish criteria for selecting filters and the frequency for changing them, as well as the generation of filter validation data. Each manufacturer must know the bioburden of the drug and the procedures required for filter integrity testing. Filters might not have to be changed after each batch is sterilized. Gather data to justify the integrity of the filters for the time used and to verify that “grow through” has not occurred.

If ethylene oxide (ETO) sterilization is used, establish what tests should be made for residues and degradation. Establish specifications for the ETO sterilization cycle, including preconditioning of the product, ETO concentration, gas exposure time, chamber and product temperature, and chamber humidity.

2. Indicators

Establish which type of indicator to use to ensure sterility (e.g., lag thermometers, peak controls, Steam Klox, test cultures, biological indicators). *Caution:* When spore test strips are used to test the effectiveness of ethylene oxide sterilization, be aware that refrigeration may cause condensation on removal to room temperature. Moisture on the strips converts the spore to the more susceptible vegetative forms of the organism which may affect the reliability of the sterilization test. The spore strips should not be stored where they could be exposed to low levels of ethylene oxide.

If biological indicators are used, assure compliance with the current USP on sterilization and biological indicators. In some cases, testing biological indicators may become all or part of the sterility testing. Biological indicators are of two forms, each of which incorporates a viable culture of a single species of microorganism. In one form, the culture is added to representative units of the lot to be sterilized or to a simulated product that offers no less resistance to sterilization than the product to be sterilized. The second form is used when the first form is not practical, as in the case of solids. In the second form, the culture is added to disks or strips of filter paper or metal, glass, or plastic beads.

Data required to establish the choice of indicator include:

- Surveys of the types and number of organisms in the product before sterilization
- Data on the resistance of the organism to the specific sterilization process
- Data used for selecting the most resistant organism and its form (spore or vegetative cell)

- Studies of the stability and resistance of the selected organism to the specific sterilization process
- Studies on the recovery of the organism used to inoculate the product

If a simulated product or surface similar to the solid product is used, the simulation or similarity must be validated. The simulated product or similar surface must not affect the recovery of the numbers of indicator organisms applied. Also, the number of organisms used to inoculate the product, simulated product, or similar surface must be validated, including stability of the inoculums during the sterilization process. Qualified personnel are crucial to the selection and application of these indicators, so their qualifications must be verified, including their experience dealing with the process, expected contaminants, testing of resistance of organisms, and technique. Written instructions regarding use, control, and testing of biological indicators by product must be available and should include a description of the method used to demonstrate the presence or absence of a viable indicator in or on the product.

Data used to support the use of the indicator each time it is used should include:

- Counts of the inoculums used
- Recovery data to control the method used to demonstrate the sterilization of the indicator organism
- Counts on unprocessed, inoculated material to indicate the stability of the inoculums for the process time
- Results of sterility testing specifically designed to demonstrate the presence or absence of the indicator organism for each batch or filling operation

Also, the way in which the organisms are handled should be observed to ensure that they do not contaminate the drug manufacturing area and product.

3. Filled Containers

Record procedures for how the filled containers leave the filling room. Is the capping or sealing done in the sterile fill area? If not, how is sterility maintained until capped? Proper filling and sealing of containers can be verified by documentation of, for example, leak and torque tests. Data on examinations made for particulate contamination should be reviewed periodically. Be aware that an FDA inspector can quickly check for suspected particulate matter by using a polariscope. Employees doing visual examinations online must be properly trained. If particle counts are done by machine, this operation must be validated.

4. Personnel Practices

The employees must be properly dressed in sterile gowns, masks, caps, and shoe coverings. Establish the gowning procedures, and be sure that good aseptic techniques are maintained in the dressing and filling rooms. Check on these practices after lunch and other absences. Is fresh sterile garb supplied, or are soiled garments reused? If the dressing room is next to the filling area, establish firm rules on how employees and supplies enter the sterile area.

I. LABORATORY CONTROLS

1. Retesting for Sterility

See the USP for guidance on sterility testing. Sterility retesting is acceptable provided the cause of the initial nonsterility is known. It cannot be assumed that the initial sterility test failure is a false positive. This conclusion must be justified by sufficient documented investigation. Additionally, spotty or low-level contamination may not be identified by repeated sampling and testing.

2. Retesting for Pyrogens

As with sterility, pyrogen retesting can be performed provided it is known that the test system was compromised. It cannot be assumed that the failure is a false positive without documented justification. All initial pyrogen test failure reports must be concluded with justification for retesting.

3. Particulate Matter Testing

Particulate matter consists of extraneous, mobile, undissolved substances, other than gas bubbles, unintentionally present in parenteral solutions. Cleanliness specifications or levels of nonviable particulate contamination must be established. Limits are usually based on the history of the process. The particulate matter test procedure and limits for LVPs in the USP can be used as a general guideline; however, the levels of particulate contamination in sterile powders are generally greater than in LVPs. LVP solutions are filtered during the filling operation, but the filling operation of sterile powders, except powders lyophilized in vials, cannot include filtration. Considerable particulate contamination is also present in sterile powders that are spray-dried due to charring during the process.

J. PRODUCTION RECORDS

Production records should be complete. Critical steps, such as integrity testing of filter, should be signed and dated by a second responsible person. Production records should ensure that directions for significant manufacturing steps are included and reflect a complete history of production.

K. OINTMENTS, LIQUIDS, AND LOTIONS

Major factors in the preparation of these drugs are the selection of raw materials, manufacturing practices, equipment, controls, and laboratory testing. Besides the basic compliance fundamentals, the following topics are of significant concern:

- Selection and compatibility of ingredients
- Whether or not the drug is a homogeneous preparation free of extraneous matter
- The possibility of decomposition, separation, or crystallization of ingredients
- The adequacy of ultimate containers to hold and dispense contents
- Procedure for cleaning the containers before filling
- Maintenance of homogeneity during manufacturing and filling operations

The most common problem associated with the production of these dosage forms is microbiological contamination caused by faulty design and/or control of purified water systems. Some of these drugs have preservatives added that protect them from microbial contamination. The preservatives are used primarily in multiple-dose containers to inhibit the growth of microorganisms introduced inadvertently during or after manufacturing. The adequacy of preservative system should be established by preservative effectiveness testing. For additional information, review the *Antimicrobial Preservatives: Effectiveness* section of the USP.

Equipment employed for manufacturing topical drugs is sometimes difficult to clean. This is especially true for those that contain insoluble active ingredients. The equipment cleaning procedures, including cleaning validation data, should be clearly established.

VI. PACKAGING AND LABELING (21 CFR, SUBPART G)

Packaging and labeling operations must be controlled so that only those drugs that meet the specifications established in the master formula records are distributed. Review in detail the packaging and labeling operations to decide if the system will prevent drug and label mix-ups. Approximately 25% of all drug recalls originate in this area, thus companies should establish controls or procedures to provide positive assurance that all labels are correct. Adequate physical separation of labeling and packaging operations from manufacturing processes requires the following policies and practices:

- Review label copy proof before it is delivered to the printer.
- Review a printer's copy of the label.
- Determine whether or not a representative of the firm will inspect the printer.
- Determine whether or not gang printing is prohibited.
- Determine whether or not labels are checked against the master label before being released to stock; make one person responsible for label review prior to release of the labels to production.
- Determine whether or not labels match specifications provided in the batch production records.
- Provide separate storage for each label (including package inserts) to avoid mix-ups.
- Inventory label stocks.
- Decide whether the printer's count is acceptable or if labels should be counted upon receipt.
- Designate one individual to be responsible for storage and issuance of all labels.
- Be sure the packaging and labeling department receives a batch record, or other record, showing the quantity of labels required for a batch.
- Decide whether the batch record will be retained by the packaging supervisor or will accompany the labels to the actual packaging and labeling line.
- Have adequate controls in place for verifying the quantities of labels issued, used, and returned.
- Account for excess labels; destroy excess labels bearing specific control codes and obsolete or changed labels.
- Inspect facilities before labeling to ensure that all previously used labeling and drugs have been removed.
- Maintain batch identification during packaging.
- Follow control procedures if a significant unexplained discrepancy occurs between quantity of drug packaged and the quantity of labeling issued.
- Segregate facilities to label one batch of the drug at a time. If this is not practiced, procedures must be in place to prevent mix-ups.
- Methods are in place for checking similar types of labels of different drugs or potencies to prevent mixing.
- Quarantine finished packaged products to permit adequate examination or testing of a representative sample to detect errors before the batch is distributed.

- Designate an individual to make the final decision that a drug should go to the warehouse or to the shipping department.
- Establish controls over the utilization of any outside firms, such as contract packers.
- Pay special attention to firms using rolls of pressure-sensitive labels, as the following can occur:
 - Paper chips cut from the label backing to help run the labels through a coder can interfere with the code printer, causing digits in the lot number to be blocked out.
 - Some rolls containing spliced sections can result in label changes in the roll.
 - Some labels shifting on the roll during printing can result in omitting required information.

The use of cut labels can cause a significant problem and should be evaluated in detail. Most firms are replacing their cut labels with roll labels. The labels of OTC products must comply with warnings required by 21 CFR 369. A control code must be used to identify the finished product with a lot or control number that permits determination of the complete history of the manufacture and control of the batch. It is important to:

- Establish the complete key (breakdown) to the code.
- Determine whether or not the batch number is the same as the control number on the finished package. If not, determine how the finished package control number relates and how it is used to find the identity of the original batch.
- Be aware that the use of gang-printed labels is prohibited unless they are adequately differentiated by size, shape, or color (21 CFR 211.122(f)).
- If cut labels are used, one of the following special control procedures must be used (21 CFR 211.122(g)):
 - Dedication of packaging lines.
 - Use of electronic or electromechanical equipment to conduct a 100% examination of finished product.
 - Use of visual inspection to examine 100% of the finished product for hand-applied labeling; the visual examination will be conducted by one person and independently verified by a second person.

Labeling reconciliation required by 21 CFR 211.125 is waived for cut or roll labeling if a 100% examination is performed according to 21 CFR 211.22(g)(2).

VII. HOLDING AND DISTRIBUTION (21 CFR, SUBPART H)

The finished product storage and shipping areas must have the sanitary conditions, stock rotation, and special storage conditions required for specific drugs. Clear records and separated stocks are maintained for any drugs that have been rejected or are on hold for other than routine reasons.

VIII. LABORATORY CONTROLS (21 CFR, SUBPART I)

Laboratory controls should include adequate specifications and test procedures to ensure that components and in-process and finished products conform to appropriate standards of identity, strength, quality, and purity. For proper laboratory controls:

- Establish a master file of specifications for all raw materials used in drug manufacture. This master file should include sampling procedures, sample size, number of containers to be sampled, manner in which samples will be identified, tests to be performed, and retest dates for components subject to deterioration.
- Form a policy about protocols of assay. These reports are often furnished by raw material suppliers; however, the manufacturer is responsible for verifying the validity of the protocols by periodically performing their own complete testing and routinely conducting identity tests on all raw materials received.
- Establish laboratory procedures for releasing raw materials, finished bulk drugs, or packaged drugs from quarantine. Establish who is responsible for this decision. Raw material specifications should include approved suppliers.
- For NDA or ANDA drugs, the approved suppliers listed in their specifications should be the same as those approved in the NDA or ANDA.
- The laboratory should be adequately staffed and equipped to do all raw material, in-process, and finished product testing that is claimed.
- Where in-process testing is done, specify what types of tests are made and whether a representative sample is obtained from various stages of processing.
- Provide specifications and descriptions of laboratory testing procedures for finished products.
- Provide procedures for checking the identity and strength of all active ingredients, including pyrogen and sterility testing, if applicable.
- If the laboratory conducts pyrogen tests, safety tests, or bioassays, determine a suitable number of laboratory animals and keep them adequately

fed and housed; provide for care on weekends and holidays.

A. STERILITY TESTING PROCEDURES

Entries should be permanently recorded and show all results, both positive and negative. Be sure that representative samples being tested are adequately recorded. When checking the sterility testing procedures, determine:

- Physical conditions of testing room; facilities used to conduct sterility testing should be similar to those used for manufacturing products
- Laboratory procedures for handling sterile sample
- Use of ultraviolet lights
- Number of units tested per batch
- Procedure for identifying test media with specific batches
- Ability of test media to support growth of organisms
- Length of incubation period
- Procedure for diluting products to offset the effects of bacteriostatic agents
- Pyrogen testing procedures

Animals involved in positive pyrogen tests should be withdrawn from use for the required period. If the Limulus Amebocyte Lysate (LAL) test is used, establish compliance according to the FDA's *Guideline on Validation of the Limulus Amebocyte Lysate Test*.

If any tests are made by outside laboratories, record the names of the laboratories and the tests they performed. Adequate controls should be in place to ensure that the laboratories' work is valid:

- Procedures should be in place to verify qualifications of individuals performing the tests and their traceability.
- For components and finished products, reserve sample programs and procedures should be evaluated. Challenge the system to determine if the samples are maintained and can be retrieved. The storage container must maintain the integrity of the product.
- Stability tests can be performed on:
 - The drug product in the container and closure system in which it is marketed
 - Solutions prepared as directed in the labeling at the time of dispensing (determine if expiration dates, based on appropriate stability studies, are placed on labels)
- If penicillin and non-penicillin products are manufactured on the same premises, non-penicillin products should be tested for penicillin contamination.

IX. CONTROL RECORDS (21 CFR 211, SUBPART J)

A. MASTER PRODUCTION AND CONTROL RECORDS (21 CFR 211.186)

The various master production and control records are important because all phases of production and control are governed by them. Master records, if erroneous, may adversely affect the product. These records must be prepared according to the drug cGMPRs outlined in 21 CFR 211.186. These records might not be in one location, but should be readily available for review.

B. BATCH PRODUCTION AND CONTROL RECORDS (21 CFR 211.188)

The batch production and control records must document each significant step in the manufacture, labeling, packaging, and control of specific batches of drugs. 21 CFR 211.188 describes the basic information that batch records must provide. A complete production and control record may consist of several separate records, which should be readily available to the investigator. Routinely check the batch record calculations against the master formula record; give special attention to those products on which there have been complaints. Be aware that transcription errors can occur from the master formula record to the batch record; be alert for transcription or photocopying errors involving misinterpretation of symbols, abbreviations, and decimal points, etc. It is important that batch production records be specific in terms of equipment (e.g., V-blender vs. ribbon blender) and processing times (e.g., mixing time and speed). The equipment should have its own unique identification number. The manufacturing process for these products must be standardized, controlled, and validated.

C. DISTRIBUTION (21 CFR 211.196)

Complete distribution records should be maintained according to 21 CFR 211.196. Be alert to shipments of products subject to abuse or which have been targeted for high-priority investigation by the FDA. These include steroids, counterfeits, and diverted drugs (e.g., physician samples, clinical packs). Check on the authenticity of orders received and establish what references are used to authenticate the identity of recipients (e.g., current editions of the AMA Directory or the Hays Directory).

D. COMPLAINT FILES (21 CFR 211.198)

21 CFR 211.198 requires maintaining records of all written and oral complaints. Although the FDA has no authority to require drug firms, except those manufacturing prescription drugs, to open their complaint files, a company should be prepared to confront the FDA on this issue. Complaint files should be readily available for review, and these records should include procedures for review and evaluation of complaint handling. Make sure that all complaints are handled as complaints and are not inappropriately excluded.

X. RETURNED DRUG PRODUCTS (21 CFR 211, SUBPART K)

Returned drugs often serve as an indication that products may have decomposed during storage or are being recalled or discontinued. Establish how returned drug items are to be handled. For example, will they be quarantined, destroyed after credit, or returned to storage? Establish who examines the returned drugs in the laboratory, and who makes the ultimate decision as to the use of the returned drugs. Dumping salvage drugs in the trash is a potentially dangerous practice in violation of U.S. Environmental Protection Agency regulations. Establish appropriate procedures for getting rid of salvage.

APPENDIX: GMP Audit Template, EU Guidelines
<http://pharmacos.eudora.org/F2/eudoralex/vol-4/home.html>

		Compliance 1 2 3*	Remarks	EU-Guide
1	PERSONNEL			
1.1	Qualified personnel available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.1
1.2	Organisation charts available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.2
1.3	Job descriptions available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.2
1.4	Responsibilities clearly defined?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.2
	<u>Key personnel</u>			
	Responsible persons designated for:			
1.5	• Production?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.5
1.6	• Quality control?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.6
1.7	Are they independent from each other?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.3
1.8	Are joint functions clearly defined?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.7
1.9	Are the responsible persons working full time?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.3
1.10	Have the responsible persons the appropriate formation, knowledge and experience?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.1/2.2
1.11	Have the relevant departments enough personnel?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.1
	<u>Training</u>			
1.12	Continuous training programmes for the production and QC staff?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.8
1.13	Initial job training for all employees?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.9
1.14	Teaching aids (videos, slides, brochures) available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.9
1.15	External training courses for the staff?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.9
1.16	Training records?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.9
1.17	Special training in sensitive areas? (sterile prod., toxic subs.)	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.10
1.18	Information for visitors to the manufacturing area?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.11
2	HYGIENE			
	<u>Personnel Hygiene</u>			
	Detailed written hygiene programmes for:			
2.1	• clothing?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.13
2.2	• use of washrooms?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.13
2.3	• behaviour in production areas?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.13
2.4	Precautions against sick or personnel with open wounds in production?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.14
	Medical examination:			
2.5	• on recruitment?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.15
2.6	• regular re-examinations?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.15

* 1. Fulfilled or available; 2. partially fulfilled; 3. not fulfilled or not available.

		Compliance 1 2 3*	Remarks	EU-Guide
	Duty of notification after:			
2.7	• trips to tropical countries?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.15
2.8	• cases of contagious illness in the family?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.15
2.9	Instructions for appropriate working clothes?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.16
2.10	Absence of food and drinks (chewing gum!) in the working area?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.17
2.11	Measures against contact with open product (gloves etc.)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.18
2.12	Instructions for hand washing in production?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.19
2.13	Change of clothes when entering and leaving the production area?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.19
2.14	Change rooms and toilets easily within reach?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.31
2.15	Toilets and restrooms sufficiently separated from production areas?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.30/3.31
2.16	Work shops separate from production areas?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.32
2.17	Laboratory animal rooms totally segregated from production rooms?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.33
3	WAREHOUSE			
	<u>Rooms, general:</u>			
3.1	Suitable for the intended use?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3
3.2	• adequate size?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3
3.3	• clean?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3
3.4	Located and designed to exclude external contamination?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.1
3.5	Appropriate level of maintenance?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.2
3.6	Maintenance works possible without contamination risk?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.2
3.7	Appropriate lighting and air conditioning?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.3
3.8	Recording of temperature and humidity?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
3.9	Protection against the entry of insects or other animals?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.4
3.10	Controlled access for authorised personnel only?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.5
	<u>Rooms, special requirements</u>			
	Type of warehousing:		
3.11	Separation of goods sufficient?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.18
3.12	Provision for different storage temperatures?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.19
3.13	Goods receiving zone weather protected?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.20
3.14	Cleaning zone for incoming goods?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.20
3.15	Separate quarantine area with controlled access?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.21
3.16	Separate, protected sampling area?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.22
	Separate and safe storage of:			
3.17	• returned goods?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.23
3.18	• rejected goods?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.23

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		Compliance 1 2 3*	Remarks	EU-Guide
3.19	Separate and safe storage of highly active, toxic or dangerous substances?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.24
3.20	Safe storage of narcotics?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.24
3.21	Safe storage of printed packaging materials?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.25
3.22	Security measurements against theft?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.25
3.23	Smoke detectors?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.25
3.24	Fire extinguishing system?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.25
	<u>Operations:</u>			
3.25	Reception, sampling and labelling according to written procedures?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.2
3.26	Is a sampling plan available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		suppl. 4
3.27	Cleaning of incoming containers?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.3
3.28	Investigation and recording of damaged deliveries?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.4
3.29	FIFO principle?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.7
3.30	Inventory system?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.8
3.31	The location of materials can be detected at all times?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
3.32	Incoming goods: containers and seals intact?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.27
3.33	Incoming goods: conformity with bill of delivery?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.27
	Labelling of incoming containers with:			
3.34	• internal name and code?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.29
3.35	• allocated batch number?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.29
3.36	• quarantine status?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.29
3.37	• expiry date or re-analysis date?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.29
3.38	Identity test for each incoming container?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.29
3.39	Are the sampled containers marked?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.30
3.40	Are reference samples taken?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.30
3.41	Safe storage of printed packaging materials?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.41
3.42	Lot tracing of all packaging materials possible?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.42
3.43	Are excessive packaging materials destroyed?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.43
	Release of starting materials by:		
	Physical/inventory checks on raw materials, packaging materials and finished goods:			
	Item:	Stocks: Physical:	Stocks: Inventory:	Storage conditions:

* 1. Fulfilled or available; 2. partially fulfilled; 3. not fulfilled or not available.

		Compliance 1 2 3*	Remarks	EU-Guide
4	DISPENSING/ASSEMBLING			
	<u>Rooms, general:</u>			
4.1	Suitable for the intended use?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3
4.2	• adequate size?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3
4.3	• clean?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3
4.4	Located and designed to exclude external contamination?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.1
4.5	Appropriate level of maintenance?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.2
4.6	Maintenance works possible without contamination risk?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.2
4.7	Appropriate lighting and air conditioning?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.3
4.8	Recording of temperature and humidity?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
4.9	Protection against the entry of insects or other animals?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.4
4.10	Controlled access for authorised personnel only?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.5
	<u>Rooms, special requirements:</u>			
4.11	Segregated from production and warehouse?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.13
4.12	Separate weighing cabins?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.13
4.13	Separate AHU for each cabin?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.12
	Air pressure gradient from weighing cabin → corridor:		3.3
4.14	Dust extraction systems available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.11
	<u>Operations:</u>			
4.15	Balances regularly calibrated?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.41
4.16	Only pharmaceutical raw materials in this area?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.17
4.17	Check on remains from previous materials before entering of new materials into a weighing cabin?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.9/5.35
4.18	Only one material in one cabin?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.9
4.19	Are dispensed materials correct labelled?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.29
4.20	Only released products in the dispensing?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.31
4.21	Cleaning SOP's for the dispensing?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.28
4.22	Previously dispensed material recorded on weighing protocol?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.8
4.23	Safety measures against mix up's during assembling (e.g. cage pallets)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.32/5.34
5	SOLIDS MANUFACTURING			
	Field of activity:			
	• Granulation	<input type="checkbox"/>		
	• Compression	<input type="checkbox"/>		
	• Encapsulation	<input type="checkbox"/>		
	• Film- and sugar coating	<input type="checkbox"/>		

* 1. Fulfilled or available; 2. partially fulfilled; 3. not fulfilled or not available.

		Compliance 1 2 3*	Remarks	EU-Guide
	• Visual inspection (Capsules, tablets etc.)	<input type="checkbox"/>		
	• Premix (Human)	<input type="checkbox"/>		
	<u>Rooms, general:</u>			
5.1	Suitable for the intended use?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3
5.2	• adequate size?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3
5.3	• clean?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3
5.4	Located and designed to exclude external contamination?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.1
5.5	Appropriate level of maintenance?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.2
5.6	Maintenance works possible without contamination risk?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.2
5.7	Appropriate lighting and air conditioning?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.3
5.8	Recording of temperature and humidity?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
5.9	Protection against the entry of insects or other animals?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.4
5.10	Controlled access for authorised personnel only?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.5
	<u>Rooms, special requirements:</u>			
5.11	Separate manufacturing area for penicillins/cephalosporins or highly sensitising substances?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.6
5.12	Only for processing of pharmaceuticals?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.6
5.13	Logical flow of materials?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.7
5.14	Walls, floors and ceilings: smooth surface and free of cracks?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.8
5.15	Easy cleaning possible?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.10
5.16	Adequate drains with traps and grilles?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.11
5.17	Appropriate air handling system?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.12
	Air pressure gradient from working bay → corridor:		
	Classification according to EC guide?		
5.18	Appropriate dust extraction system?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.14
5.19	Appropriate lighting?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.16
5.20	Separate rest rooms?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.30
5.21	Changing rooms designed to avoid contamination?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.31
5.22	Toilets segregated from manufacturing areas?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.31
	<u>Equipment</u>			
5.23	Suitable for the intended use?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.34
5.24	Well maintained?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.34
5.25	Written & validated cleaning procedures?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.36
5.26	Maintenance without contamination risk (sep. area)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.35
5.27	Equipment in contact with product: suitable materials quality?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.39
5.28	Machinery equipped with measuring and control devices?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.40

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		Compliance 1 2 3*	Remarks	EU-Guide
5.29	Calibration in fixed intervals acc. to written procedures?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.41
5.30	Calibration records available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.41
5.31	Contents and flow direction marked on pipes?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.42
5.32	Pipes for distilled and demineralized water regularly monitored and sanitised?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.43
5.33	Not functioning equipment in the production area (if yes: clearly marked)?	Y N <input type="checkbox"/> <input type="checkbox"/>		3.44
5.34	Status of cleanliness indicated?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.13
5.35	Previous product indicated?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.13
	Operations			
5.36	Are written and validated procedures for all manufacturing steps available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.2
5.37	Are all manufacturing steps recorded with actual parameters?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.2
5.38	Check of each single container of the starting materials (contents, weight, identity)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.3
5.39	Limits for yields?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.8
5.40	Only one batch of one product processed?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.9
5.41	Protection against microbial contamination?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.10
5.42	Appropriate measures against generation of dust (e.g. closed systems)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.11
	Correct labelling of containers, materials, equipment and rooms with:			5.12
5.43	• product name and batch no.	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.12
5.44	• quarantine status?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.12
5.45	Deviations from standard procedures recorded and signed by the supervisor?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.14
5.46	Special procedures for the production of antibiotics, hormones etc.?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.19
5.47	• Campaign production?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.19
5.48	• Special monitoring?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.19
5.49	• Validated decontamination procedure?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.19
5.50	Double check on weight?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.34
5.51	Line clearance before start of production?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.35
5.52	Investigation of deviations in yields?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.39
5.53	Validated procedures for reworking of rejected batches?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.62
5.54	Detailed procedures for the addition of previous batches?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.63
5.55	Special release procedure (QA) for those batches?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.64
5.56	Use of protective clothing (hair cover, shoes, masks, gloves)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.16
5.57	Clothing regulation for visitors?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.11
	IPC			5.38
	Who performs IPC?		
5.58	Are IPC methods approved by QC?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.18

* 1. Fulfilled or available; 2. partially fulfilled; 3. not fulfilled or not available.

		Compliance 1 2 3*		Remarks		EU-Guide
	Performance of IPCs:	During Start-up?		Frequency	Automatic data recording?	
		Yes	No		Yes No	
	<u>Tablets/Kernels</u>					
5.59	Individual weights	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	
5.60	Disintegration	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	
5.61	Thickness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	
5.62	Hardness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	
5.63	Friability/Abrasion	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	
	<u>Sugar/Film coated tablets</u>					
5.64	Weights	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	
5.65	Disintegration	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	
5.66	Residual absolute humidity (IR or)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	
	<u>Capsules</u>					
5.67	Individual weights	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	
5.68	Disintegration	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	
	<u>Validation</u>					
5.69	Validation according to fixed procedures?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		5.21
5.70	New procedures released only after validation?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		5.22
	Validation of changes of:					
5.71	• processes?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		5.23
5.72	• starting materials?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		5.23
5.73	• equipment?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		5.23
5.74	Revalidation in fixed intervals?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		5.24
5.75	Procedures for the retrospective validation of old procedures?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
6	LIQUIDS MANUFACTURING					
	Operations carried out:					
	• Dispensing (if different from solid)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
	• Syrups and suspensions	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
	• Drops	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
	• Ointment manufacture	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
	• Ointment filling	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
	• Ampoule solution manufacture	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
	• Sterile or aseptic ampoule filling	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		

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		Compliance 1 2 3*	Remarks	EU-Guide
	• Sterile freeze drying	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
	• Sterile powder filling	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
	<u>Rooms, general:</u>			
6.1	Suitable for the intended use?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3
6.2	• adequate size?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3
6.3	• clean?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3
6.4	Located and designed to exclude external contamination?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.1
6.5	Appropriate level of maintenance?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.2
6.6	Maintenance works possible without contamination risk?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.2
6.7	Appropriate lighting and air conditioning?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.3
6.8	Recording of temperature and humidity?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
6.9	Protection against the entry of insects or other animals?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.4
6.10	Controlled access for authorised personnel only?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.5
	<u>Rooms, special requirements:</u>			
6.11	Separate manufacturing area for penicillins/cephalosporins or highly sensitising substances?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.6
6.12	Only for processing of pharmaceuticals?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.6
6.13	Logical flow of materials?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.7
6.14	Walls, floors and ceilings: smooth surface and free of cracks?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.8
6.15	Easy cleaning possible?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.10
6.16	Adequate drains with traps and grilles?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.11
6.17	Appropriate air handling system with filtered air where open products are exposed to the environment?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.12
	Air pressure gradient from working bay → corridor:		
	Classification according to EC guide?		
6.18	Appropriate lighting?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.16
6.19	Separate rest rooms?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.30
6.20	Changing rooms designed to avoid contamination?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.31
6.21	Toilets segregated from manufacturing areas?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.31
	<u>Equipment</u>			
6.22	Suitable for the intended use?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.34
6.23	Well maintained?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.34
6.24	Tanks, containers, pipework and pumps designed for easy cleaning and sanitation (dead legs!)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		Suppl. § 2
6.25	Written & validated cleaning procedures?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.36
6.26	Maintenance without contamination risk (sep. area)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.35
6.27	Equipment in contact with product: suitable materials quality?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.39

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		Compliance 1 2 3*	Remarks	EU-Guide
6.28	Machinery equipped with measuring and control devices?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.40
6.29	Calibration in fixed intervals acc. to written procedures?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.41
6.30	Calibration records available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.41
6.31	Contents and flow direction marked on pipes?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.42
6.32	Pipes for distilled and demineralized water regularly monitored and sanitised?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.43
6.33	Not functioning equipment in the production area (if yes: clearly marked)?	Y N <input type="checkbox"/> <input type="checkbox"/>		3.44
6.34	Status of cleanliness indicated?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.13
6.35	Previous product indicated?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.13
	<u>Operations</u>			
6.36	Are written and validated procedures for all manufacturing steps available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.2
6.37	Are all manufacturing steps recorded with actual parameters?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.2
6.38	Check of each single container of the starting materials (contents, weight, identity)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.3
6.39	Limits for yields?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.8
6.40	Only one batch of one product processed?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.9
6.41	Protection against microbial contamination?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.10
	Correct labelling of containers, materials, equipment and rooms with:			5.12
6.42	• product name and batch no.	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.12
6.43	• quarantine status?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.12
6.44	Deviations from standard procedures recorded and signed by the supervisor?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.14
6.45	Special procedures for the production of antibiotics, hormones, etc.?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.19
6.46	• Campaign production?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.19
6.47	• Special monitoring?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.19
6.48	• Validated decontamination procedure?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.19
6.49	Double check on weight?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.34
6.50	Line clearance before start of production?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.35
6.51	Investigation of deviations in yields?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.39
6.52	Specification of max. storage time and storage conditions if products are not immediately filled or packaged?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		Suppl. § 9
6.53	Validated procedures for reworking of rejected batches?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.62
6.54	Detailed procedures for the addition of previous batches?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.63
6.55	Special release procedure (QA) for those batches?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.64
6.56	Use of protective clothing (hair cover, shoes, masks, gloves)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.16
6.57	Clothing regulation for visitors?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.11
	<u>Water</u>			
6.58	Loop system for purified water?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		Suppl. § 4

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		Compliance 1 2 3*	Remarks	EU-Guide
6.59	Antimicrobial treatment of purified water?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		Suppl. § 4
6.60	Loop system for water for injection?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		Suppl. § 4
	Storage temperature of water for injection:		Suppl. § 4
6.61	Loop system constructed to avoid deadlegs?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		Suppl. § 4
6.62	Regular microbiological monitoring?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		Suppl. § 4
6.63	Regular endotoxin control?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		Suppl. § 4
	<u>Special requirements for sterile and aseptic products</u>			Suppl.
	<u>Rooms and equipment</u>			
6.64	Access of staff and materials to clean areas <i>only</i> through air-locks?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		1
6.66	Rooms classified according EC-Guide?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3
	Classification for products to be sterilised:			
6.67	• Solution preparation (EC: class C, with special precautions class D):	Class:		5
6.68	• Filling (EC: under LF in class C):	Class:		5
	Classification for aseptic products:			
6.69	• Handling of starting materials that can be sterile filtered (EC: class C):	Class:		6
6.70	• Handling of starting materials that cannot be sterile filtered (EC: class A in class B):	Class:		6
6.71	• Handling and filling of bulk (EC: class A in Class B):	Class:		6
6.72	All rooms easy to clean/disinfect?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		17
6.73	Doors, windows, frames, lighting etc. without edges?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		18
6.74	Suspended ceilings (if yes: sealed?)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		19
6.75	Traps constructed to avoid microb. contamination?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		21
6.76	Appropriate constructed changing rooms?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		22
6.77	Measures against opening of both doors of air-locks?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		23
6.78	Overpressure gradient from cleanest areas to others?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		24
6.79	AHU validated and regularly revalidated?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		25
6.80	Control instruments for pressure gradient?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		26
6.81	Warning system for errors in air supply?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		26
6.82	Recording of pressure gradients?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		26
6.83	Do conveyor belts leave sterile areas?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		28
6.84	Maintenance works outside from clean areas possible?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		28
6.85	Cleaning and disinfection procedure after maintenance works?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		29
6.86	Regular revalidation of all equipment and systems?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		30
6.87	Water prepared, circulated and stored to exclude microb. contamination?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		31
6.88	Cleaning and disinfection of rooms according to validated SOPs rooms?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		32
	• Disinfection methods?		
6.89	Microb. monitoring of cleaning and disinfection agents?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		33

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		Compliance 1 2 3*	Remarks	EU-Guide
6.90	Microb. monitoring programme of production areas?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		35
6.91	Results recorded and considered for the release?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		35
	<u>Personnel and Hygiene</u>			
6.92	Minimal no. of personnel in clean areas?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		7
6.93	Special and regular training?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		8
6.94	Regular medical examinations?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		10
6.95	Appropriate clean room clothes (material, design)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		12
6.96	Protective clothes worn correctly?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		12
6.97	Prohibition of cosmetics, jewellery and watches?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		13
6.98	New clean room clothes for each working cycle?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		15
6.99	Appropriate washing and sterilisation of clothes?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		16
	<u>Operations</u>			
6.100	Validation (media filling) in regular intervals?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		38
	Monitoring of water preparation system, frequency:			
6.101	• microbiological:		40
6.102	• chemical:		40
6.103	• particles:		40
6.104	• endotoxins:		40
6.105	Microbiological monitoring of starting materials?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		42
6.106	Max. storage times defined for sterilised equipment?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		45
6.107	Max. storage time defined between solution preparation and filtration?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		46
6.108	Material transfer to clean areas through double door autoclaves?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		48
	<u>Sterilisation processes</u>			
6.109	All processes validated?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		50
6.110	Sterilised and not sterilised materials clearly separated?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		54
	Trays and boxes clearly labelled with:			
6.111	• Product name and code	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		54
6.112	• Batch no.	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		54
6.113	• Status: sterilised or not sterilised	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		54
	Sterilisers:			
6.114	• Recording of temp., pressure and time?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		55
6.115	• Coldest point determined?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		55
6.116	• Independent counter check probe?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		55
6.117	• Heat-up time for each product determined?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		56
6.118	• Sterile cooling media?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		57
6.119	• Tightness tests for vacuum autoclaves?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		58

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		Compliance 1 2 3*	Remarks	EU-Guide
6.120	• Clean steam for steam autoclaves?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		58
6.121	• Circulated air with over-pressure?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		61
6.122	• Recirculated air: sterile filtered?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		61
6.123	• Ethylene oxide autoclaves: humidity, temp. and time recorded?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		69
6.124	• Ethylene oxide autoclaves: use of bioindicators?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		70
	<u>Filtration</u>			
6.125	Double filtration?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		75
6.126	Integrity testing of filters immediately after use?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		77
6.127	Are results part of the batch protocol?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		77
6.128	Optical control of each single container of ampoules, vials and infusions?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		82
	<u>IPC</u>			
6.129	Written IPC procedures and SOPs?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
	Particle testing of:			
6.130	• Rooms	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
6.131	• Primary packaging materials	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
6.132	• System of warning and action limits?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
	Microbiological monitoring of:			
6.133	• Rooms			
6.134	• Personnel			
6.135	• Equipment			
6.136	Residual O ₂ of ampoules, infusions and syrups?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
6.137	Endotoxin testing of water and packaging materials?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
6.138	Calibration of equipment?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
6.139	Regular revalidation of equipment?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
7	PACKAGING			
	Operations carried out:			
	• Blistering	<input type="checkbox"/>		
	• Foil-packaging	<input type="checkbox"/>		
	• Filling into tablet glasses	<input type="checkbox"/>		
	• Effervescent Packaging	<input type="checkbox"/>		
	• Powder filling	<input type="checkbox"/>		
	• Syrup/drops filling	<input type="checkbox"/>		
	• Ointment filling	<input type="checkbox"/>		
	<u>Rooms</u>			
7.1	Suitable for the intended use?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3

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		Compliance 1 2 3*	Remarks	EU-Guide
7.2	• adequate size?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3
7.3	• clean?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3
7.4	Located and designed to exclude external contamination?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.1
7.5	Appropriate level of maintenance?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.2
7.6	Maintenance works possible without contamination risk?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.2
7.7	Appropriate lighting and air conditioning?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.3
7.8	Recording of temperature and humidity?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
7.9	Protection against the entry of insects or other animals?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.4
7.10	Controlled access for authorised personnel only?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.5
7.11	Adequate separation of the packaging lines?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.15
	<u>Operations</u>			
7.12	Only <i>one</i> product per line?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.44
7.13	Check list for clearance before processing a new product/new batch?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.45
7.14	Adequate labelling of the lines (product name and code)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.46
7.15	Check of all materials delivered to the line (quantity, identity, conformity with order)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.47
7.16	Cleaning of primary packaging materials?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.48
7.17	Immediate labelling after filling?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.49
7.18	Careful check of all printing processes (code, expiry date)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.50
7.19	Special safety measures for off-line printing?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.51
7.20	Regular checks of all control devices (code reader, counter etc.)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.52
7.21	Printings clear and durable?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.53
7.22	Balancing of printed packaging materials and bulk?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.56
7.23	Destruction of excessive coded packaging material after completion of an order?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.57
7.24	Are the finished products kept in quarantine until final release?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.58
7.25	Appropriate storage after release?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.60
	<u>IPC</u>			
7.26	Checks on identity of bulk and packaging materials?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.47
	Regular line checks on:			
7.27	• Aspect of the packages	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.54a
7.28	• Completeness	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.54b
7.29	• Conformity of quantity and quality of materials with packaging order	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.54c
7.30	• Correct imprint	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.54d
7.31	• Correct function of control devices	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		5.54d
	Are the following IPC checks performed?			
7.32	• Leaking	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		

* 1. Fulfilled or available; 2. partially fulfilled; 3. not fulfilled or not available.

		Compliance 1 2 3*	Remarks	EU-Guide
7.33	• Release torque of screw caps	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
7.34	• pH, density, drop weight, viscosity, sedimentation	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
8	DOCUMENTATION			
	<u>Specifications</u>			
8.1	Specifications for raw/packaging materials available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.10
	Do they include:			
8.2	• internal name and code	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.11
8.3	• name of supplier and/or manufacturer?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.11
8.4	• reference sample (printed pack. mat.)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.11
8.5	• sampling procedure?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.11
8.6	• qualitative/quantitative specifications with limits?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.11
8.7	• storage conditions?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.11
8.8	• maximum storage period?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.11
	<u>Goods receiving?</u>			
8.9	Written procedures for the reception of deliveries?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.19
	Do records receipt include:			
8.10	• product name on labels and delivery note?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.20
8.11	• internal name and code?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.20
8.12	• receiving date?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.20
8.13	• name of supplier and/or manufacturer?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.20
8.14	• batch number of supplier?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.20
8.15	• total quantity and number of containers?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.20
8.16	• allocated internal batch number?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.20
8.17	SOPs for labelling, quarantine and storage conditions of all incoming goods available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.21
	Sampling procedures (SOPs) include:			
8.18	• authorised sampling personnel?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.22
8.19	• methods, equipment and quantities?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.22
8.20	• safety measures?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.22
	<u>Master formulae</u>			
8.21	Are master formulae for each product and batch size available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.3
8.22	Is the master formula approved and signed by the authorised persons?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.3
	The master formula includes:			
8.23	• product name and code?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.14a
8.24	• description of galenical form, dosage and batch size?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.14b

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		Compliance 1 2 3*	Remarks	EU-Guide
8.25	• all active ingredients with name, code and weight?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.14c
8.26	• all excipients used during manufacture with name, code and weight?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.14c
8.27	• yields with limits?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.14d
	Does the working procedure include:			
8.28	• the production line?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.15a
8.29	• equipment to be used?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.15a
8.30	• reference to methods for cleaning, assembling and calibration of machines?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.15b
8.31	• detailed stepwise manufacturing prescription?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.15c
8.32	• IPCs to be performed with limits?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.15d
8.33	• precautions to be followed?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.15e
8.34	Are batch records kept for each batch processed?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17
	Do batch records include:			
8.35	• Protocol of line clearance?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17
8.36	• Name of the product and batch no.?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17a
8.37	• Date and time of start and end of production?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17b
8.38	• Name and initials of responsible workers for each step?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17c,d
8.39	• Batch and analytical no. and actual weight of all starting materials?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17e
8.40	• Equipment used?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17f
8.41	• Results of IPCs with initials of person who carries them out?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17g
8.42	• Yields of the relevant manufacturing steps?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17h
8.43	• Detailed notes on problems and process deviations?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17i
8.44	Records on reprocessing of batches?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
	<u>Packaging instructions:</u>			
8.45	Packaging instructions for each product, package size and presentation?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.16
	Do they include:			
8.46	• Product name?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.16a
8.47	• Description of galenical form and strength?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.16b
8.48	• Package size?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17c
8.49	• List of all packaging materials with code for a standard batch size?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17d
8.50	• Samples of printed packaging materials?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17e
8.51	• Special precautions?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17f
8.52	• Description of the process and equipment?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17g
8.53	• IPCs to be performed with sampling instruction?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.17h
8.54	Are packaging batch records kept for each batch or part batch?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18
	Do the packaging batch records include:			
8.55	• Protocol of line clearance?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18
8.56	• Name of the product?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18a

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		Compliance 1 2 3*	Remarks	EU-Guide
8.57	• Date and time when operations have been performed?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18b
8.58	• Name of the responsible person?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18c
8.59	• Initials of workers carrying out operations?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18d
8.60	• Notes on identity checks and conformity with packaging instructions?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18e
8.61	• Results of IPCs	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18e
8.62	• Details of operations and equipment used?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18f
8.63	• Samples of printed packaging materials with codes (MFD, EXP, Batch no. etc.)?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18g
8.64	• Record of problems and process deviations?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18h
8.65	• Quantities of packaging materials delivered, used, destroyed or returned?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18i
8.66	• No. of packs consumed?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.18j
	Testing			
	Do the written testing procedures include:			
8.67	• Test methods?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.23
8.68	• Equipment for testing?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.23
8.69	Tests documented?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.23
	Others			
8.70	Procedures for release and rejection of materials and finished products?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.24
8.71	Final release by authorised person?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.24
8.72	Records about distribution of each batch?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.25
	Procedures and protocols about:			
8.73	• Validation?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.26
8.74	• Set up and calibration of equipment?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.26
8.75	• Maintenance, cleaning and disinfection?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.26
8.76	• Training records?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.26
8.77	• Environmental monitoring of production areas?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.26
8.78	• Pest control?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.26
8.79	• Complaints?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.26
8.80	• Recalls?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.26
8.81	• Returned goods?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.26
8.82	Instructions for use of manufacturing and testing equipment?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.27
	Log books for major equipment incl. date and name of persons who performed:			
8.83	• Validation?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.28
8.84	• Calibration?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.28
8.85	• Maintenance, cleaning and repair works?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.28
8.86	Chronological records of use of major equipment and manufacturing areas?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		4.29

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		Compliance 1 2 3*	Remarks	EU-Guide
9	QUALITY CONTROL			6
	<u>General requirements</u>			
9.1	Independent QC department available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.1
9.2	Head of QC well qualified and sufficiently experienced?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.1
9.3	Qualified personnel available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.1
9.4	Organisation charts available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.2
9.5	Job descriptions available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.2
9.6	Responsibilities clearly defined?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.2
9.7	Continuous training programmes for QC staff?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.2
9.8	Initial job training for all employees?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		2.9
9.9	Training records?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
9.10	QC personnel admitted to the production rooms for sampling etc.?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
	<u>QC Laboratories</u>			
9.11	Suitable for the intended use?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.26
9.12	Laboratories of adequate size?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.26
9.13	Appropriate level of maintenance?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.1
9.14	Adequate separation from the production area?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.26
9.15	Controlled access of authorized personnel only?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.5
9.16	Special laboratory to handle biological samples available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.29
9.17	Special laboratory to handle radioactive material available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.29
9.18	Separate recreation rooms for the personnel available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.30
9.19	Animal laboratories present?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.33
9.20	Animal laboratories separated from other areas?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.33
9.21	Animal laboratories equipped with a separate air handling system?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		3.33
	<u>QC Documentation</u>			
9.22	Do procedures exist for self inspection? release or rejection of products or raw material? product complaints? product recalls? local stability testing? storage of reference samples? validation of analytical procedures?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
9.23	Specifications available for raw materials? bulk products? packaging materials?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.7
9.24	Analytical procedures for every product?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		

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		Compliance 1 2 3*	Remarks	EU-Guide
9.25	Are Basel methods followed?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
9.26	Validation of locally developed test methods?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
9.27	Sampling procedures available for raw materials? bulk products? packaging materials?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.7
9.28	Suppliers certificates available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.7
9.29	Calibration programme for analytical instruments installed?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.7
9.30	Maintenance programme for analytical instruments?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.7
9.31	Retention system for QC records?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.8
9.32	Batch documents stored for expiry + 1 year or 5 years (EEC 75/319, article 22) minimum?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.8
9.33	Are original data like notebooks stored in addition to the batch documents?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.10
9.34	Can the original data be traced back easily and quickly from the analytical report number or batch number?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.10
9.35	Are trend analyses being performed for analytical results? yields? environmental monitoring data?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.9
	Sampling			
9.36	Written procedures for taking samples?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.11
9.37	Do procedures define method of sampling? necessary equipment? quantity of the sample? subdivision of the sample? sample container? labelling of samples? storage conditions? cleaning and storage of sampling equipment? identification of containers sampled	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
9.38	Are samples representative for the batch they are taken from? (sampling plan)	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.12
9.39	Are critical steps being surveilled and validated by additional sampling (for example beginning or end of a process).	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.12
9.40	Sample containers labelled with name of the content batch number date of sampling batch containers sampled	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.13
9.41	Are samples taken by QC/QA?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
9.42	Reference samples retained for validity plus 1 year?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.14
9.43	Storage of reference samples under the recommended storage conditions?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.14
9.44	Finished products stored in the final packaging?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.14

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		Compliance 1 2 3*	Remarks	EU-Guide
9.45	Quantity of the reference sample makes 1 (better 2) complete reanalysis possible?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.14
9.46	Sample room secure?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
9.47	Sample room neatly organized and not overcrowded?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
	Testing			
9.48	Are the applied analytical methods validated?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.15
9.49	Analytical methods in compliance with the registration?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.16
9.50	Are all results recorded and checked for correctness?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.16
9.51	Are all calculations checked?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.16
9.52	Do the testing protocols contain name and galenical form of material? batch number? supplier if applicable? specification reference? method reference? analytical results? reference to analytical certificates? date of the analysis? name of the analyst? name of the person verifying the data? statement of release or rejection? date and sign of the release person?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.17
9.53	Are all IPC methods in production approved by QC?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.18
9.54	Are written methods available for the preparation of reagents and volumetric solutions?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.19
9.55	Is a record maintained of standardisation of volumetric solutions?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.2
9.56	Are reagents for prolonged use labelled with date of the preparation? sign of the preparator?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.20
9.57	Are unstable reagents labelled with expiry date? storage conditions?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.20
9.58	Are volumetric solutions labelled with the last date of standardisation? last current factor?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.20
9.59	Are reference standards labelled with name and potency suppliers reference date of receipt date of expiry	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		6.21
9.60	Are reference standards stored properly and under the control of a designated person?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		
9.61	Are animals used for testing of components, materials or products quarantined before use? checked for suitability? Are records maintained showing the history of their use?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		

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		Compliance 1 2 3*	Remarks	EU-Guide
10	COMPLAINTS AND PRODUCT RECALLS			8
	<u>Complaints</u>			8.1
10.1	Does a written complaint procedure exist?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		8.2
10.2	Are product complaints carefully reviewed?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		8.1
10.3	Is a person designated to handle complaints and to decide on measures to be taken?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		8.1
10.4	Is each complaint concerning a product recorded with all original details?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		8.3
10.5	Are product complaints thoroughly investigated?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		8.3
10.6	Is a responsible person of QC involved in the study?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		8.3
10.7	Is it considered that other batches might be concerned as well?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		8.4
10.8	Are decisions and measures as a result recorded?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		8.5
10.9	Is this record added to the corresponding batch documents?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		8.5
10.10	Are the complaint records regularly revised with respect to specific or reoccurring problems?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		8.6
10.11	Are the authorities informed of serious quality problems with a product?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		8.7
	<u>Recalls</u>			8.8
10.12	Does a written recall procedure exist?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		8.9
10.13	Is a person nominated responsible for the execution and coordination of a recall?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		8.8
10.14	Responsible person independent of the marketing and sales organization?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		8.8
10.15	Are the competent authorities informed of an imminent recall?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		8.11
10.16	Does the person responsible for a recall have access to the distribution records?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		8.12
10.17	Do the distribution records contain sufficient information on customers with addresses? phone numbers inside or outside working hours? batches and amounts delivered? medical samples?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		8.12
10.18	Are recalled products stored separately in a secure area?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		8.13
10.19	Is a final record made including a reconciliation between the delivered and recovered quantities?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		8.14
10.20	Is the effectiveness of the arrangements for recalls checked critically from time to time?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		8.15
11	SELF INSPECTION			9
11.1	Does a self inspection procedure exist which defines frequency and programme?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		9.1
11.2	Are self inspections carried out to check compliance with GMP rules?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		9.1

* 1. Fulfilled or available; 2. partially fulfilled; 3. not fulfilled or not available.

		Compliance 1 2 3*	Remarks	EU-Guide
11.3	Are self inspections conducted in an independent and detailed way? by designated competent persons from the company or external experts?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		9.2
11.4	Are self inspections recorded?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		9.3
11.5	Do reports contain the observations made during a self inspection? proposals for corrective measures?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		9.3
11.6	Are actions subsequently taken recorded?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		9.3
12	CONTRACT MANUFACTURE AND ANALYSIS			7
12.1	Written contract between contract giver and contract acceptor available?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		7.1
12.2	Are responsibilities and duties clearly defined?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		7
12.3	All arrangements in accordance with the marketing authorization of the product concerned?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		7.2
	<u>The contract giver</u>			
12.4	Competence of the acceptor to carry out the work successful and according to GMP assessed?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		7.3
12.5	Acceptor provided with all the informations necessary to carry out the contract work?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		7.4
12.6	Acceptor informed of safety aspects?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		7.4
12.7	Conformance of products supplied by the acceptor ensured?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		7.5
12.8	Product released by a qualified person on the acceptor's side?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		7.5
	<u>The contract acceptor</u>			
12.9	Does the acceptor have adequate premises and equipment? knowledge and experience? competent personnel? a manufacturing authorization?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		7.6
12.10	Does the acceptor ensure that all products or materials delivered to him are suitable?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		7.7
12.11	There must be no work passed to a third party without the permission of the giver.	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		7.8
12.12	If a third party is involved it must have the necessary manufacturing and analytical information.	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		7.8
	<u>The contract</u>			
12.13	Does the written contract specify the responsibilities?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		7.10
12.14	Have technical aspects been drawn up by competent persons?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		7.10
12.15	Release of material and check for compliance with the marketing authorization defined?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		7.11

* 1. Fulfilled or available; 2. partially fulfilled; 3. not fulfilled or not available.

		Compliance 1 2 3*	Remarks	EU-Guide
12.16	Is defined who is responsible for purchasing of materials? IPC controls testing and release of materials? manufacturing and quality control? sampling? storage of batch documentation?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		7.12
12.17	Are manufacturing, analytical and distribution records available to the contract giver?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		7.13
12.18	Contract permits the giver to visit the facilities of the acceptor?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		7.14
12.19	In the case of contract analysis: Does the contract acceptor understand that he is subject to inspection by the competent authorities?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		7.15
13	AUDIT OF SUPPLIERS			2.7
13.1	Supplier audits performed for excipients? active substances? packaging material?	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>		

* 1. Fulfilled or available; 2. partially fulfilled; 3. not fulfilled or not available.

2 Solid Oral Dosage Forms

I. INTRODUCTION

The *Validation Guidelines* issued by the Food and Drug Administration (FDA) in 1987 defines process validation as establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes. The three components of this definition include:

- Documented evidence
- Consistency
- Predetermined specifications

Documented evidence includes the experiments, data, and analytical results that support the master formula, the in-process and finished product specifications, and the filed manufacturing process.

With regard to consistency, several batches would have to be manufactured, using the full-scale batch size, to demonstrate that a process meets the consistency test. At least three batches are needed to demonstrate consistency.

The development of a product and its manufacturing process and specifications, the design of the validation protocol, and the demonstration (validation) runs of the full-scale manufacturing process requires scientific judgment based on good scientific data. The FDA expects that in-process control and product specifications will be established during the product development process, with the test batch serving as the critical batch used for the establishment of specifications.

Specifications, such as hardness and particle size, should be established prior to validation of the process; these specifications should be included in the validation protocol. Problems often arise when the product development runs of the process are used to establish both specifications and demonstrate that the system is validated. In these cases, more in-depth inspection and evaluation will be required; some of these process runs often produce failing product because the product specifications have not been fully established and tested.

II. BACKGROUND

Two common complaints regarding validation issues have frequently been raised. The first concerns the misconception that the 1987 *Validation Guideline* represents a new requirement. The second concerns the lack of specificity

in the FDA's guides. In 1978, however, the Current Good Manufacturing Practice Regulations (cGMPRs) were revised and provided for process validation, so this guideline does not represent a new requirement.

Both the FDA and the industry have recognized the need to establish general guidance for the validation of manufacturing processes, and the FDA published a draft guideline in 1983. However, this draft guideline was a very general document that addressed general principles and was applicable to both sterile and nonsterile drugs and devices. In 1984, the guideline was reissued as a draft guideline and was finalized in 1987. The 1987 *Validation Guidelines* merely points out the need to adequately develop and control manufacturing processes. It discusses microbiological issues and provides few specific and practical applications for the validation of manufacturing processes for a marketed solid oral dosage form.

The issue of retrospective validation and its application to marketed products is frequently encountered. This concept of using historical data (test results), along with process control and process specificity was of value until more scientific methods for demonstrating process validation evolved. It should be pointed out that retrospective validation is not merely the review of test results. It also requires that the manufacturing process be specific and the same each time a batch is manufactured. Thus, specific raw-material specifications (including particle size when necessary), in-process specifications (tablet hardness, etc.), and specific manufacturing directions are required. Obviously, any failing batches attributed to the process would necessitate the conclusion that the process is not validated and is inadequate.

Prospective process validation is required, particularly for those products introduced in the last 7 to 8 years or those for which manufacturing changes have been made; however, in some cases where older products have been on the market without sufficient premarket process validation, it may be possible to validate, in some measure, the adequacy of the process by examination of accumulated test data on the product and records of the manufacturing procedures used.

III. PRODUCT DEVELOPMENT

A. PRODUCT DEVELOPMENT REPORTS

No statute or regulation specifically requires a product development report, although companies are required to

produce scientific data that justify the formulation and the manufacturing and control processes. Most companies use product development reports, technology transfer reports, and others to summarize the scientific data that justify the product and process. The product development report should satisfy the needs of the company. No specific format is required for the contents of the report.

It is suggested that a company develop a product development standard operating procedure (SOP) that describes the development process, the documentation requirements, and the individuals responsible for approving the filed process. This SOP can be brief, and again no legal requirement exists stating that companies must produce such an SOP. Failure to have a formal development report is not a GMP deficiency, nor is it a filing requirement to have a formal development report; however, where such reports *are* written, the development data found in these reports should include the following.

1. Drug Substance Characterization

Characterization of the chemical and physical properties of the drug substance is one of the most critical steps in the development of a solid dosage form. Chemical properties, especially the identification of impurities, are very important. In addition, the physical properties of the API, such as solubility, polymorphism, hygroscopicity, particle size, density, etc., must be addressed. The literature and actual experience demonstrate that the physical quality (e.g., particle size of raw materials), can sometimes have a significant impact on the availability and clinical effect of a dosage-form drug; therefore, it is appropriate that the physical characteristics of a drug substance be characterized, that the impact of the physical characteristics be determined, and that a specification for the bulk drug product be established, if necessary.

Development data will vary between new drugs and generics (e.g., characterization and establishment of specifications for the drug substance). In most cases, the manufacturing process for a new drug substance (new chemical entity) is developed and scaled-up before the dosage form. In early development stages very little information is available regarding polymorphic forms, solubility, etc. Consequently, changes to the manufacturing process for the drug substance may change the purity profile or physical characteristics and thus cause problems with the finished dosage form. Although these types of problems are expected, the firm must investigate and document batch failures for the API and dosage form product.

On the other hand, generic manufacturers usually purchase drug substances from API manufacturers who may not be willing to supply information regarding the synthesis or analysis of the drug substance; therefore, the manufacturer of the finished dosage form must perform the appropriate tests to characterize the drug substance chemically

and physically and establish appropriate specifications. This may require developing analytical methods to identify impurities. In some cases, this information can be obtained from literature searches.

In either case, it is important that each firm compare the drug substance used to manufacture the bio-batch or clinical batch(es) and the drug substances used for the commercial batches, including specifications, analytical methods, and test results for the lots of each drug substance. Remember that the safety of the drug may be based upon the type and level of impurities, and different physical characteristics may affect dissolution or content uniformity. This is particularly important for those drug substances that are poorly soluble in water.

For those products on which biostudies have been conducted, the physical characteristics of the drug substance used for the study should serve as the basis for the physical specifications.

It is widely recognized that when discussing *in vivo* release rates and drug absorption rates, fast and immediate release is not always best. For some “immediate”-release drug products, such as carbamazepine tablets, a slower release is desired; therefore, it is frequently desirable to have minimum and maximum particle size specifications to control the release rate. For example, micronizing or milling a drug substance to provide a greater surface area of the substance may also result in faster dissolution and possibly faster absorption and higher blood levels. Such changes to improve the dissolution may not always be desired.

In addition to release or dissolution, variation in particle size, particle shape, and/or bulk density can also have an effect on the uniformity of dosage forms, particularly those manufactured by direct compression or direct encapsulation.

Particulate solids, once mixed, have a tendency to segregate by virtue of differences in the shape, size, and density (other variables are also important) of the particles of which they are composed. This process of separation occurs during mixing, as well as during subsequent handling of the completed mix. Generally, large differences in particle size, density, or shape within the mixture result in instability in the mixture. The segregation process normally requires energy input and can be reduced following mixing by careful handling.

Some manufacturers establish wide ranges for specifications. These must be established based on a GMP and validation perspective. Even though a wide range for a physical specification, such as particle size or surface area, may be established in a filing, it is expected that such ranges will be verified during validation of the process. In a recent court decision, the judge ruled that companies cannot hide behind approval of processes listed in an application when these processes do not work. In other words, the approval of a filing has no impact on processes

that do not perform consistently. For example, in a particular filed process it was determined that particle size would have no effect on drug absorption and dissolution, and a wide-range particle size specification was established; however, during the GMP review, it was found that variation in particle size did have a major effect on content uniformity. Therefore, a tighter particle size specification had to be established.

Control of the physical characteristics of the excipient is also important because variations in such characteristics may also affect the performance of the dosage form. Changes in particle size of some excipients, for example, may affect content uniformity. In other cases, a change in the supplier of an excipient or lubricant may affect dissolution or bioavailability. In fact, the release of the active ingredients in some products is timed by varying lubricant blending time and concentration. The literature contains many examples of lubricant processing causing major changes. Such changes in excipients illustrate deficiencies with the utilization of retrospective validation; for such validation to be satisfactory, control of all parameters and key steps in the process is necessary.

The control of mixing times and physical characteristics of all ingredients is critical to successful validation of all formulations and processes. A major question that must be addressed is the need for testing physical characteristics (particle size) for each batch of excipient. For many single-source excipients, particle size is a supplier specification and is usually tightly controlled. Having established a specification and not testing each lot of excipient upon receipt may be satisfactory in such cases; however, for some multisource excipients and where the dosage formulator expects to shift sources of supply, some resulting differences in physical characteristics (particle size) may have an effect on dose uniformity and dissolution. Definite justification should exist for not testing lots of excipients for physical characteristics.

2. Manufacturing Procedures

Procedures used to manufacture development batches must be specific and well documented. This is necessary for scale-up and subsequent comparison to the commercial process. This is another area where differences between New Drug Application (NDA)/New Animal Drug Application (NADA) and Abbreviated New Drug Application (ANDA)/Abbreviated New Animal Drug Application (ANADA) products arise. In the case of the NDA/NADA, there will be several clinical and/or test batches manufactured over a period of time showing changes in the process as more is learned about the drug and the process. The level of documentation should increase as the process becomes more defined and the firm begins phase II and III studies.

The generic product focus is on the biobatch. Again, the process used to manufacture the biobatch must be well defined and well documented; test batches must be manufactured to establish that biobatch manufactured is reproducible.

3. In-Process Testing

Specific specifications required to control the manufacturing process must be established and justified. Doing so will require granulation studies, including blend uniformity, sieve analysis, and moisture.

4. Finished Product Testing

Testing for standards given in FDA monographs such as content uniformity (when a specification applies), assay, hardness, friability, dissolution, and others are essential.

5. Dissolution Profile

The dissolution profiles for the biobatch or pivotal clinical batches should be evaluated in the product development report. Good correlation should exist between the dissolution specifications and test results for the biobatch/clinical test batches and the full-scale commercial process.

6. Stability

The Center for Drug Evaluation and Research (CDER) conducts an evaluation of stability data and approves proposed expiration dates. The product development report should contain an evaluation of the stability data that have been obtained. During post-approval inspections, stability data are reviewed by the field. An FDA inspection, therefore, inevitably includes an audit of underlying raw data and analytical worksheets to ensure the accuracy and authenticity of stability data contained in summary reports.

B. PRE-APPROVAL INSPECTIONS

Validation of three full-size commercial lots is not required for approval of the marketing application; however, the firm must have data that justify the full-scale commercial process filed in the NDA/ANDA or NADA/ANADA application. In other words, the firm should have sufficient research on the test batches to establish specifications for the manufacturing and control procedures listed in the application. These data and specifications form the basis for the validation protocol that may be developed following approval of the application. The final step in the process is demonstration (validation) runs to prove that the process will perform consistently. Firms should validate the process using the specifications listed in the filing. To evaluate the proposed manufacturing process,

the following areas must be covered during the pre-approval inspection.

1. Master Formula

This document must include specific manufacturing directions for the full-scale commercial process, including in-process and finished product specifications. Make sure that the process filed in the application complies with the process used to manufacture the bio/clinical batch. In some cases, the process may be different after scale-up. This is acceptable if the firm has data showing the product produced by this process will be equivalent. Data such as granulation studies, finished product test results, and dissolution profiles are used to document that the two processes are equivalent.

2. History Section of the Application

This section of the application is used to identify the biobatch or batches used for pivotal clinical studies. Any batches in which *in vivo* studies were carried out, particularly those for which *in vivo* studies showed a lack of equivalency, are subject to review.

3. Development Data (Product Development Report)

The firm cannot logically proceed to the validation step without some prior evaluation of the process. During the development phase, the critical process parameters must be identified and specifications established. These predetermined specifications must be established during the development of the process, with the biobatch or pivotal clinical batch serving as the reference batch.

Development of a solid dosage form will vary from firm to firm and will be dependent upon the specific product and process; however, the formula ranges, physical and chemical specifications of the drug substance and excipients, in-process variables, interaction effects of the dosage form ingredients under normal and stress aging conditions should be confirmed by limited challenge in pilot-scale and production-size batches.

Such development data serve as the foundation for the manufacturing procedures, specifications, and validation of the commercial process. In some cases, manufacturers establish specifications such as hardness and particle size during validation; however, as the validation definition states, specifications must be determined prior to validation of the process.

When a manufacturer files a manufacturing process in an application, the FDA expects that the process will yield a product that is equivalent to the product on which the biostudy or pivotal clinical study was conducted; therefore, it is important that the development and scale-up of

the process be well documented so that a link between the bio/clinical batches and the commercial process can be established. The firm should have data such as granulation studies, finished product test results, and dissolution profiles that may be used to document that the two processes are equivalent.

In most cases *in vitro* data alone will not be sufficient to document equivalency. The bioequivalency evaluation must be made by qualified individuals, and the firm should have a signed statement documenting that the processes are equivalent.

4. Inspection of the Facilities

The FDA inspectors physically inspect the facility to ensure that the area and ancillary equipment such as air-handling and water systems are suitable for the proposed manufacturing process. Construction of new walls, installation of new equipment, and other significant changes must be evaluated for their impact on the overall compliance with GMP requirements. These inspections include facilities used for development batches and to be used for full-scale production batches.

5. Raw Materials

The FDA inspectors review the information contained in the raw materials section of the product development report. Inventory records are a good source for identification of batches used for product development and biostudies.

6. Laboratory

The regulatory inspection of a laboratory involves observations of the laboratory in operation and of the raw laboratory data to evaluate compliance with GMPs and to specifically carry out the commitments in an application or Drug Master File (DMF). The raw laboratory data, laboratory procedures and methods, laboratory equipment, and methods validation data must be periodically reviewed to ensure overall quality of the laboratory operation and the ability to comply with GMP regulations.

It is not uncommon for the FDA inspecting team to identify foreign peaks and impurities not filed or discussed in applications. Also, many inspections reveal laboratory test methods that are not validated. The transfer of laboratory methods and technology from the research and development department to the quality control department should be firmly established. Be aware that FDA inspectors are not bound by any rules to restrict their investigation to particular product files. They can and often do pick up data files, charts, and recordings that are lying around in the area and will raise queries. It is a good idea to keep these records properly secured to avoid unnecessary distractions in the inspection process.

7. Equipment

At the time of the pre-approval inspection, the FDA expects that the equipment will be in place and qualified. New products, particularly potent drug products, can present cleaning problems for existing equipment. Manufacturers must validate their cleaning processes for the new drug/dosage form.

IV. VALIDATION PROTOCOLS

Validation protocols are developed from the information obtained during product development research. These protocols list the specific manufacturing process and specifications that will be tested during the demonstration runs. Validation protocols are not required for the Pre-Approval Inspection but are required for Post-Approval Inspections. Key processes and control specifications should have been established during product development research and should be carefully listed in the validation protocol.

V. DEMONSTRATION RUNS (VALIDATION OF THE PROCESS)

A. TEST BATCH RELATIONSHIPS

A validated process should produce a dosage form that is directly related to the dosage form on which equivalency and/or efficacy and safety data were determined. This is usually the test batch; therefore, ensure that the process used to make the test batch has been used for routine full-scale production batches. These processes and specifications must be equivalent, and the importance and need for good control of the manufacturing process used to produce the test and clinical batches cannot be overemphasized. Typically, the control of test batches includes, among other components, drug substance characterization, granulation analyses, and dose uniformity and dissolution profiles. The validation report should compare the manufacturing processes and specifications for the test batches to those for the full-scale batches; however, such findings may be contained in other documents, such as bioequivalency reports, and should be readily available.

B. POST-APPROVAL PROSPECTIVE VALIDATION INSPECTIONS

In the post-approval, pre-marketing phase, the FDA reviews the validation protocol and validation report. Obviously, a validation protocol that lists all of the variables and parameters that should be controlled when the process is validated cannot be written until the variables are identified in the development phase. In many of the FDA's post-approval, pre-marketing inspections, validation (and consistency) are often not well established. Failures of

production-size batches include dissolution, lack of content uniformity, and variable potency. Validation reports on batch scale-ups may also reflect selective reporting of data. Several parameters must be considered when ensuring validation of the manufacturing process for an oral solid dosage form. For example, at least eight major areas must be evaluated:

- Biobatch relationship
- Raw materials
- Manufacturing procedures and equipment
- Granulation/mix analysis
- In-process controls
- Test results with validated methods
- Investigations/product failures
- Site review

1. Raw Materials

Physical characteristics of raw materials can vary among manufacturers of drug substances and, on occasion, have varied from lot to lot from the same manufacturer. The examination of retained samples of the lots of raw materials can reveal physical differences between the two lots and thus should become a routine measure. A quantitative compliance must be present for the raw material inventory records to evaluate the use of the drug substance in biobatch, clinical, and/or test batches. Make sure to account for the quantities and sources of materials used and the testing performed. Physical specifications for drug substances should be well established. If no such specifications are available, or only a very vague specification is, support data should exist to demonstrate that dissolution profiles and content uniformity will be satisfactory over a wide range of particle sizes. For example, a manufacturer may establish a specification that 90% of the particles must be less than 300 microns. For validation of this process, one would expect the use of micronized as well as nonmicronized material with particles close to 300 microns in size.

2. Manufacturing Procedures and Equipment

Regardless of the nature of the specificity of the manufacturing directions contained in the application, a detailed master formula with specific manufacturing directions and specifications must have been developed before any validation protocol is prepared and before the validation process begins. The basic premise of validation of a process is that a detailed process already exists that, it is hoped, will be shown to perform consistently and produces products in compliance with predetermined specifications; therefore, detailed manufacturing directions specifying equipment and operating parameters must be specified in the master formula.

The importance of specific written directions and specifications cannot be overemphasized. For example, problem areas include:

- Failure to specify the amount of granulating solution, resulting in overwetting and dissolution failures of aged batches
- Failure to specify the encapsulation machine and operating parameters, such as dosing discs, resulting in weight variation failures
- Failure to specify the compression machine(s) and operating parameters, resulting in content uniformity failures

In addition to the concern about specific manufacturing directions, equipment presents its own set of unique problems that have to be considered in the control of the manufacturing and the validation processes. The following is a brief description of some issues associated with equipment.

a. Blenders

Many solid oral dosage forms are made by direct compression. The two types of mixers are low energy and high energy. The low-energy mixers represent the classical type of slow mixers, such as ribbon blenders, tumblers, and planetary pony pan; the high-energy mixers include some basic features of the low-energy mixers but also contain some type of high-speed blade, commonly termed an intensifier bar or chopper. The various types of mixers can be described as follows:

1. *Pony pan type.* This mixer has historically been used for the manufacture of wet granulations. Because of its open pan or pot, granulating agents such as starch paste can be added while mixing. Because the pan is open at the top to allow the mixing blades to penetrate the powder, mixing operations are usually dusty and can lead to potential cross-contamination problems. The usefulness of these mixers is limited to wet granulating. This type of mixer provides good horizontal (side-to-side) blending; however, vertical (top-to-bottom) mixing does not occur. Powder placed in the mixer first will be poorly mixed. Segregation or unmixing is also a recognized problem. To minimize this problem, some manufacturers have emptied the pan contents half-way through the mixing cycle in an attempt to turn the powder over at the bottom of the mixer. To alleviate the problem of the lack of mixing along the sides or walls of the pan, manufacturers have utilized a hand-held steel paddle at various times during mixing. This type of mixing is difficult to control and reproduce; thus, it would be difficult to validate.

The potential for segregation and poor mixing along the sides and particularly the bottom of the pony blender makes this type of blender less desirable for the dry blending of granulations of drug products; consequently, whenever such dry blending is encountered, investigators will look for potential problems with blending validation and content uniformity. Whenever in-process samples of the granulation are collected as part of an investigation or inspection, the formula card and the weight of the dosage unit to be manufactured are needed for the calculations.

2. *Ribbon blender.* In the ribbon blender, powder is mixed both horizontally and vertically. Loading operations can be dusty, but during the actual blending the unit is enclosed, thereby limiting the amount of dust released to the environment. The major and potentially the most serious problem with the ribbon blender is the “dead spot” or zone at the discharge valve in some of these blenders. To compensate for this dead spot, manufacturers have to recycle the powder from this area at some point during the mixing process. Obviously, adequate and very specific directions and procedures should be available to ensure that this critical step is performed. Another concern with this mixer is the poor mixing at the ends of the center horizontal mixing bar and at the shell wall because of blade clearance. The level of powder placed in this mixer is normally at the top of the outer ribbon blade, and, as with other mixers, care must be taken not to overfill the mixer. Cleaning problems, particularly at the ends of the ribbon blender where the horizontal bar enters the blender, have been identified. Manufacturers who do not disassemble and clean the seals/packing between batches should have data to demonstrate the absence of foreign contaminants between batches of different products processed in the blender.
3. *Tumbler blender.* Common mixers of this type include the twin shell and double cone. These mixers exert a gentle mixing action; because of this mild action, lumps of powder will not be broken up and mixed. Powders may also clump due to static charges and segregation can occur. Low humidity can contribute to this problem. Blending under very dry conditions has been found to lead to charge build-up and segregation, while blending of some products under humid conditions has led to lumping. More so than with other mixers, powder charge levels should not exceed 60 to 65% of the total volume of the mixer. Fabricators of tumbler-type blenders

identify the volume as the actual working capacity and not the actual volume of the blender. It is important to correlate the bulk density of the granulation with the working capacity of the blender.

4. *High-shear (high-energy) mixers.* The several fabricators of these mixers include GRAL, Diosna, and Littleford/Lodige. These mixers are highly efficient and ideally suited for wet granulations. End points of wet granulations can be determined by measurements on a gauge of the work required to agitate the blend. The mixing vessel is enclosed, and dust only enters the environment when loading. One of the problems associated with these mixers is the transfer or conversion of products blended in the older types of mixers to these blenders. Mixing times are going to be different, and the physical characteristics of the blend may also be different. These mixers are very efficient. For wet granulations, it is important to control the rate and amount of addition of the solvent. Because of their efficiency, drug substance may partially dissolve and recrystallize upon drying as a different physical form. An intensifier bar in the center of the blender rotates at very high speeds to break down the smaller, harder agglomerates. A major disadvantage of this type of blender is that the extremely high speed of the intensifier bar generates considerable heat, which can sometimes result in charring of some sugar-based granulations. It should be pointed out that these same comments are applicable to other high-energy mixers that also rely on high-speed choppers to disperse powders. Also, cleaning of the blender requires disassembly of the intensifier bar between products.
5. *Plastic bag.* Any discussion of mixers would not be complete without addressing the plastic bag. Firms have resorted to the blending or manufacture of a trituration in a plastic bag. Obviously, it is very difficult to reproduce such a process, and there is the potential for loss of powder as a result of breakage or handling. The use of a plastic bag cannot be justified in the manufacture of a pharmaceutical product. When the plastic bag has been used, directions are usually not specific, and one would not know by reading the directions that a plastic bag was employed. Some companies have been known to hide the use of plastic bags by indicating in the manufacturing records that a blender was used; these bags are easy to spot during an inspection, and the practice is highly discouraged.

b. Dryers

The two basic types of dryers are the oven dryer, in which the wet granulation is spread on trays and dried in an oven, and the fluid-bed dryer, in which the wet granulation is “fluidized” or suspended in air. Generally, the fluid-bed dryer yields a more uniform granulation with spherical particles; however, this may result in compression problems that may require additional compression force. It is not unusual to see manufacturers change from an oven dryer to the fluid-bed dryer; however, such a change should be examined for equivalency with *in vitro* testing such as hardness, disintegration, and comparative dissolution and stability testing.

Other issues of concern with drying include moisture uniformity and cross contamination. Tray dryers present more moisture uniformity problems than fluid-bed dryers. Obviously, a dryer should be qualified for heat uniformity and a program developed to ensure moisture uniformity in granulations at the end point of drying. With respect to fluid-bed dryers, moisture problems can occur if the granulation is not completely fluidized.

In regard to cross-contamination, oven dryers, particularly those in which air is recirculated, present cross-contamination problems because air recirculates through a common filter and duct. For fluid-bed dryers, the bag filters present cross-contamination problems. In order to minimize such problems, manufacturers should use product-dedicated bags.

c. Tablet and Capsule Equipment

Another important variable in the manufacturing process is the tablet press or encapsulating machine. The newer dosage form equipment requires granulations with good flow characteristics and good uniformity. The newer tablet presses control weight variation by compression force and require a uniform granulation to function correctly. Setup of the microprocessor controlled tablet press usually includes some type of challenge to the system. For example, a short punch is sometimes placed among the other punches. If the press is operating correctly, it will alarm when a lower or higher weight tablet is compressed.

Different tablet compression equipment can cause dose uniformity, weight uniformity, and hardness problems. For example, vibrations during tablet compression can cause segregation of the granulation in the feed hopper. The speed of the machine can affect the fill of the die and tablet weight; therefore, as previously noted, it is important to have specific operating directions.

Many unit operations now provide for blending in totes, with direct discharge of the tote into the tablet compression equipment. Because of segregation problems at the end of the discharge, tablets from the end of the compression should be tested for content uniformity. The use of inserts in totes has been shown to minimize segregation.

With regard to the newer computer-controlled tablet compression equipment, buckets of tablets are often rejected because of potential weight variation problems. The disposition of these tablets, as well as the granulation and tablets used to set up the press, should be documented, and reworking processes must be validated.

With regard to encapsulation operations, the hygroscopic nature of gelatin capsules and some of the granulations require humidity controls for storage of the empty capsules and their subsequent filling. Scale-up of capsule products has also presented some problems because of the different types of encapsulation equipment. Older equipment that operated on gravity fill, such as Lilly and Parke-Davis machines, was commonly used for manufacturing capsules in clinical manufacturing areas. When formulations were scaled-up to high-speed encapsulation equipment, flow problems and weight variation resulted. Additionally, some of the newer equipment provides for the formation of a slug which could have an impact on dissolution.

Many firms, in order to recondition (rework) batches, pass those particular batches through a sorter, such as the MOCON VERICAP®. This machine works on the principal of current (dielectric constant), and moisture variation in the filled capsules can cause inaccurate results. Manufacturers should qualify equipment and examine equipment logs for these sorting machines to identify batches with weight problems. Data supporting the accuracy of equipment in regard to rejecting low- or high-weight capsules should be available during an FDA inspection.

d. Coating Equipment

Many tablets are now coated with an aqueous film coat that is usually very soluble. Current technology provides for fixed sprays of the coating solution. The volume of coating solution, rate, and temperature can be controlled by some of the more highly automated operations; however, for many sugar-coated, enteric-coated, and delayed-release products, some components of the coating are not highly soluble and that part of the process is performed manually. Generally, the shellac undercoat used for sugar-coated tablets has presented disintegration/dissolution problems, particularly in aged samples.

With respect to poor disintegration, the example of ferrous sulfate tablets probably represents the classical example. Over the years, many different manufacturers have issued recalls for poor disintegration of coated ferrous sulfate tablets; likewise, problems with poor dissolution have been attributed to the coating process. Again, the shellac undercoat hardens and even sometimes cracks, resulting in poor dissolution.

On many occasions the coating process has not been validated. The number of applications of coats, volume of coating solution in a specific application, and temperature of the solution during application are all parameters that must be addressed. For example, the temperature of

application and even heat during drying has been found to cause dissolution failures in aged tablets.

Another problem associated with the coating process concerns heat applied to products that are sensitive to heat. For example, it has been shown that estrogen tablets are heat sensitive and have exhibited stability problems; thus, it is important to control this phase of the process.

For a few products, such as some of the antihistamine tablets or multivitamin tablets containing folic acid or cyanocobalamine, the drug substance is applied during the coating process. Some products require the active drug substance to be applied as a dust on tacky tablets as part of the coating process; for these products, it is particularly important to apply the drug in the coating solution through controlled applications. Again, it is important as part of the validation of these processes to demonstrate dose uniformity and dissolution and to control the parameters of the coating process.

3. Granulation/Mix Analysis

A critical step in the manufacture of an oral solid dosage form is the blending of the final granulation. If uniformity is not achieved at this stage, then one could assume that some dosage units would not comply with uniformity requirements. The major advantage of blend analysis (from a uniformity perspective) is that specific areas of the blender that have the greatest potential to be nonuniform can be sampled. This is particularly true of the ribbon-type blender and planetary or pony-type mixers.

In some cases, such as for large or tumbler-type blenders, it is impractical to sample from the blender directly. In such cases, granulations or blends could be sampled at the time of blender discharge or directly from drums. If sampling from drums, samples from the top, middle, and bottom of each drum should be collected.

In most cases, sampling thieves are readily available for sampling the small quantities that need to be taken from key areas of the blender or the drums. If samples larger than one dosage unit must be collected, however, adequate provisions must be made to prevent excessive handling manipulation between the time of sampling and the time of analysis.

Good science and logic would seem to dictate that sample sizes of the approximate equivalent weight of the dosage unit should be sampled in order to test for uniformity. Many industrial pharmacy and engineering texts confirm this approach. Large granulation sample sizes (e.g., 1 oz) will provide little information with respect to uniformity. Generally, further mixing after sampling and prior to analysis can yield misleading results.

The acceptance criteria for granulation dose uniformity testing must be established. Although many firms evaluate dose uniformity using the compendial dose uniformity specifications (85 to 115% with a relative standard deviation

[RSD] of 6 to 7.8), such specifications should be tighter where supported by the firm's historical data on the level of blend uniformity with its equipment for a given product. In many cases, compendial assay limits for the finished product (90 to 110% of label claim) are broad enough for this purpose, and most firms should be able to demonstrate blend assay results well within these limits. If larger sample sizes are taken for assay to evaluate total composite assay, then the specific U.S. Pharmacopeia (USP) or filed criteria for assay should be used.

In addition to analysis of blends for dose uniformity and potency, blends are tested for physical characteristics. A major physical parameter used to demonstrate equivalence between batches is the particle size profile. This is particularly important for comparison of the biobatch with production batches and also when processes are modified or changed. The particle size profile will provide useful information for demonstrating comparability.

Particle size profiles are particularly important for tablets made by a wet granulation process. The size and even the type of granule can affect the pore size in a tablet and have an effect on dissolution. For example, a recent dissolution failure was attributed to a change in the milling screen size, yielding a granulation with larger granules. It was a coated tablet, and the larger pores permitted increased penetration of the coating solution into the tablet, resulting in slower dissolution.

Another test that is typically performed in regard to granulation, particularly when the wet granulation process is used, is loss on drying (LOD) and/or moisture content. If organic solvents are employed, then residual solvent residues are also tested. To validate a drying process, LOD levels are determined prior to, during, and after drying in order to demonstrate times and levels. As with processing variables, levels (specifications) are established in the development phase, with the validation phase being used to confirm the adequacy of the process.

4. In-Process Testing

In-process testing is testing performed on dosage forms during their compression/encapsulation stages to ensure consistency throughout these operations. For tablets, individual tablet weight, moisture, hardness (compression force), and disintegration tests are performed. For capsules, individual weight and moisture tests are performed. In many of the validation reports, it has been found that manufacturers have neglected to supply results of individual (not composite) dosage unit weight tests that should be performed throughout compression/encapsulation. Such testing is particularly important for capsule products, which may exhibit weight variation problems. If not part of the validation reports, the individual dosage unit weights should be recorded and be available for FDA inspectors to review.

With regard to individual capsule weights, a major question that arises concerns acceptable levels. Because most USP assay limits are 90 to 110%, it would seem reasonable that each unit manufactured complies with these specifications. It should be pointed out that 85 to 115% limits are established by the USP for variability in both blending and compression or encapsulation operations.

Because hardness and disintegration specifications are established during development and biobatch production, testing is performed to demonstrate both equivalency (comparability) and consistency.

With regard to moisture, some tablets set up upon aging as a result of poor moisture control and inadequate specifications. For example, this has been shown to be a major problem with carbamazepine tablets and often for ferrous sulfate tablets.

5. Test Results

Finished product testing, particularly assay, content uniformity, and dissolution, should be carefully recorded. With regard to dissolution, it is important to establish dissolution profiles. Validation batches with dissolution profiles not comparable to biobatches indicate nonequivalency of the manufacturing process. Depending on the discriminating nature of the dissolution test, it may also indicate lack of equivalence of the dosage forms made during validation with the biobatch. In the review of dissolution test results, it is important to eventually see results very close to 100% dissolution. In some cases, manufacturers will profile the dissolution results only to the specification; however, if lower but still acceptable results are obtained (such as 85%), it is important to continue the test by increasing the speed of the apparatus. If a product completely dissolves, yet only results in a value of 85%, it may indicate some problem with the test. Likewise, high dissolution results (115%) also indicate some problem with the test. Obviously, unusual or atypical results should be explained in the validation report.

6. Investigations and Product Failures

In any process validation exercise, a basic objective is to prove that a process is satisfactory; unfortunately, some processes are unsatisfactory and may sometimes yield unacceptable results. It is important, therefore, that when the final validation report is reviewed, all results, including failing results, are discussed and evaluated. Historically, reviews of manufacturing processes typically show that one out of every eight batches manufactured has failed content uniformity testing. Manufacturers often recognize that the process is unsatisfactory and not validated, but fail to draw this conclusion in the written validation report. This is a dangerous precedence and is often easily identified during FDA inspections.

7. Site Review

A major aspect and possibly the most critical phase of process validation is the review of data to ensure that

failing batches were not omitted without justification. Additionally, manufacturers must ensure that the raw data, including analytical raw data, are accurate.

3 Oral Solutions and Suspensions

I. INTRODUCTION

The manufacture and control of oral solutions and oral suspensions present unique problems to the industry. While bioequivalency concerns are minimal (except for antibiotic suspensions, for example), other issues have led to recalls, including microbiological, potency, and stability problems. Additionally, because the population using these oral dosage forms includes newborn, pediatric, and geriatric patients who may not be able to take oral solid dosage forms and may be compromised, defective dosage forms can pose an even greater risk than for other patients.

II. FACILITIES

The design of production facilities is largely dependent on the type of products manufactured and the potential for cross-contamination and microbiological contamination. For example, facilities used for the manufacture of over-the-counter (OTC) oral products might not require the isolation that a steroid or sulfa product would require. The manufacturer must establish policies of isolation of processes to minimize contamination. It should be further established whether or not particular drug substances and powdered excipients generate dust, given the method of manufacture used. System design and efficiency of dust removal system must be considered. A firm's heating, ventilation, and air-conditioning (HVAC) system requires particular attention, especially where potent or highly sensitizing drugs are processed. Some manufacturers recirculate air without adequate filtration. Where air is recirculated, a firm's data must demonstrate the efficiency of air filtration through surface and/or air sampling.

III. EQUIPMENT

Equipment should be of a sanitary design and should include sanitary pumps, valves, flow meters, and other equipment that can be easily sanitized. Ball valves, packing in pumps, and pockets in flow meters have been identified as sources of contamination. In order to facilitate cleaning and sanitization, manufacturing and filling lines should be identified and detailed in drawings and standard operating procedures (SOPs). In some cases, long delivery lines between manufacturing areas and filling areas have been a source of contamination. The SOPs of many manufacturers have been found to be deficient, particularly

with regard to time limitations between batches and for cleaning. Equipment used for batching and mixing of oral solutions and suspensions is relatively basic. Generally, these products are formulated on a weight basis with the batching tank on load cells so that a final QS (quantity sufficient) can be made by weight. Volumetric means, such as using a dipstick or line on a tank, have been found to be inaccurate. In most cases, manufacturers will assay samples of the bulk solution or suspension prior to filling. A much greater variability has been found with batches that have been manufactured volumetrically rather than by weight.

The design of the batching tank with regard to the location of the bottom discharge valve also presents problems. Ideally, the bottom discharge valve should be flush with the bottom of the tank. In some cases, valves (including undesirable ball valves) are several inches below the bottom of the tank; in others, the drug or preservative is not completely dissolved and lays in the dead leg below the tank, with initial samples being found to be subpotent. For the manufacture of suspensions, valves should be flush.

With regard to transfer lines, they are generally hard piped and easily cleaned and sanitized. In some cases, manufacturers have used flexible hoses to transfer product, but it is not unusual to find flexible hoses on the floor, thus significantly increasing the potential for contamination. Such contamination can occur when operators pick up or handle the hoses, possibly even placing them in transfer or batching tanks after picking them up from the floor. It is also a good practice to store hoses in a way that allows them to drain rather than coiling them, which may allow moisture to collect and be a potential source of microbial contamination.

Another common problem occurs when a manifold or common connection is used, especially in water supply, premix, or raw material supply tanks. Such common connections have been shown to be a source of contamination.

IV. RAW MATERIALS

Physical characteristics, particularly the particle size of the drug substance, are very important for suspensions. As with topical products in which the drug is suspended, particles are usually very fine to micronized (less than 25 μm). For syrups, elixirs, or solution dosage forms in which

nothing is suspended, the particle size and physical characteristics of the raw materials are not that important; however, they can affect the rate of dissolution of such raw materials during the manufacturing process. Raw materials of a finer particle size may dissolve faster than those of a larger particle size when the product is compounded.

V. COMPOUNDING

In addition to a determination of the final volume (QS) as previously discussed, microbiological concerns also exist. For oral suspensions, an additional concern is uniformity, particularly because of the potential for segregation during the manufacture and storage of the bulk suspension, during transfer to the filling line, and during filling. A manufacturer's data should support storage times and transfer operations. Procedures and time limits for such operations should be established to address the potential for segregation or settling, as well as other unexpected effects that may be caused by extended holding or stirring.

For oral solutions and suspensions, the amount and control of temperature are important from a microbiological as well as a potency aspect. For those products in which temperature is identified as a critical part of the operation, the manufacturer should maintain documentation of temperature, such as by control charts.

Some manufacturers rely on heat during compounding to control the microbiological levels in product. For such products, the addition of purified water to a final QS, the batch, and the temperatures during processing should be documented and available for review.

In addition to drug substances, some additives, such as paraben, are difficult to dissolve and require heat. The control and monitoring of their dissolution during the compounding stage should be documented. From a potency aspect, the storage of product at high temperatures may increase the level of degradants. Storage limitations (time and temperature) should be justified by manufacturers and are likely to be evaluated during an inspection.

Some oral liquids are sensitive to oxygen and have been known to undergo degradation. This is particularly true of the phenothiazine class of drugs, such as perphenazine and chlorpromazine. The manufacture of such products might require the removal of oxygen such as by nitrogen purging. Additionally, such products might also require storage in sealed tanks, rather than in tanks with loose lids. In the OTC category, the entire line of vitamins is subject to degradation if they are not properly protected against oxidation, particularly those products that contain minerals (which might contain highly active trace elements that catalyze degradation of vitamins).

VI. MICROBIOLOGICAL QUALITY

Microbiological contamination of some oral liquids can present significant health hazards. For example, some oral liquids, such as nystatin suspension, are used for infants and immunocompromised patients, and microbiological contamination with organisms such as Gram-negative organisms is objectionable. For other oral liquid preparations, such as antacids, *Pseudomonas* sp. contamination is also objectionable; however, for some oral liquids, such as cough preparations, contamination with *Pseudomonas* sp. might not present the same health hazard. Obviously, the contamination of any preparation with Gram-negative organisms is not desirable.

In addition to the specific contaminant being objectionable, such contamination would be indicative of a deficient process as well as an inadequate preservative system. The presence of a specific *Pseudomonas* sp. may also indicate that other plant or raw material contaminants could survive the process. For example, the fact that a *Pseudomonas putida* contaminant is present could also indicate that *Pseudomonas aeruginosa*, a similar source organism, could also be present.

VII. ORAL SUSPENSION UNIFORMITY

Liquid products in which the drug is suspended (and not in solution) present manufacturer control problems. Depending upon the viscosity, many suspensions require continuous or periodic agitation during the filling process. If delivery lines are used between the bulk storage tank and the filling equipment, some segregation may occur, particularly if the product is not viscous. Inspectors will review a manufacturer's procedures for filling and diagrams for line setup prior to the filling equipment. Good manufacturing practice would warrant testing bottles from the beginning, middle, and end to assure that segregation has not occurred. Such samples should not be composited or pooled. In-process testing for suspensions might also include an assay of a sample from the bulk tank. More important, however, may be testing for viscosity.

VIII. PRODUCT SPECIFICATIONS

Important specifications for the manufacture of all solutions include assay and microbial limits. Additional important specifications for suspensions include particle size of the suspended drug, viscosity, pH, and in some cases dissolution. Maintaining an appropriate viscosity is important from a processing perspective to minimize segregation. Additionally, viscosity has also been shown to be associated with bioequivalency. The pH may also have some meaning regarding effectiveness of preservative systems and may even have an effect on the amount of drug in solution. With regard to dissolution, at least several

products have dissolution specifications listed in their U.S. Pharmacopeia (USP) monographs. Particle size is also important, and at this point it would seem that any suspension should have some type of particle size specification.

IX. PROCESS VALIDATION

As with other products, the amount of data required to support the manufacturing process will vary from product to product. Development (data) should identify critical phases of the operation, including the predetermined specifications that should be monitored during process validation. For example, for solutions the key aspects that should be addressed during validation include assurance that the drug substance and preservatives are dissolved. Parameters such as heat and time should be measured. In-process assay of the bulk solution during and/or after compounding according to predetermined limits is also an important aspect of process validation. For solutions that are sensitive to oxygen and/or light, dissolved oxygen levels would also be an important test. Again, the development data and the protocol should provide limits. The manufacture of suspensions presents additional problems, particularly in the area of uniformity. Again, development data should address the key compounding and filling steps that ensure uniformity. The protocol should provide for the key in-process and finished product tests, along with their specifications. For oral solutions, bioequivalency studies may not always be needed; however, oral suspensions, with the possible exception of some antacids and OTC products, usually require a bioequivalency or clinical study to demonstrate effectiveness. As with oral solid dosage forms, comparison to the biobatch is an important part of validating the process.

X. STABILITY

One area that has presented a number of problems includes maintaining the stability of oral liquid products throughout their expiry period. Vitamins with fluoride oral liquid

products have had a number of recalls because of vitamin degradation. Drugs in the phenothiazine class, such as perphenazine, chlorpromazine, and promethazine, have also shown evidence of instability. Good practice for this class of drug products would include quantitation of both the active and primary degradant. Dosage form manufacturers should know and have specifications for the primary degradant. These manufacturers' data and validation data for methods used to quantitate both the active drug and degradant are likely to be reviewed during an inspection. Because interactions of products with closure systems are possible, liquids and suspensions undergoing stability studies should be stored on their side or inverted in order to determine whether contact of the drug product with the closure system affects product integrity. Moisture losses that can cause the remaining contents to become super-potent and microbiological contamination are other problems associated with inadequate closure systems.

XI. PACKAGING

Problems in the packaging of oral liquids have included potency (fill) of unit dose products and accurate calibration of measuring devices such as droppers that are often provided. The USP does not provide for dose uniformity testing for oral solutions. Thus, unit-dose solution products should deliver label claims within the limits described in the USP. Inspectors will review a manufacturer's data to ensure uniformity of fill and test procedures to ascertain that unit dose samples are being tested. Another problem in the packaging of oral liquids is a lack of cleanliness of containers prior to filling. Fibers and even insects have been identified as debris in containers, particularly plastic containers used for these products. Many manufacturers receive containers shrink-wrapped in plastic to minimize contamination from fiberboard cartons. Some manufacturers may utilize compressed air to clean containers, in which case vapors (such as oil vapors) from the compressed air have occasionally been found to present problems.

4 Validation of Cleaning Process

I. INTRODUCTION

Validation of cleaning procedures has generated considerable discussion since Food and Drug Administration (FDA) documents, including the *Inspection Guide for Bulk Pharmaceutical Chemicals* and *Biotechnology Inspection Guide*, have briefly addressed this issue. These FDA documents clearly establish the expectation that cleaning procedures (processes) must be validated. It is recognized that for cleaning validation, as with validation of other processes, more than one way might exist to validate a process. In the end, the test of any validation process is whether or not scientific data show that the system consistently does as expected and produces a result that consistently meets predetermined specifications. The discussion in this chapter is intended to cover equipment cleaning for chemical residues only. While cleaning validation in the manufacture of over-the-counter (OTC) products may not be as great a concern as for the manufacture of other drugs, it is an important component of current good manufacturing practices (cGMPs) that requires reiteration, which is why this chapter has been included in a book dealing with OTC drugs.

II. BACKGROUND

For the FDA to require that equipment be clean prior to use is nothing new. The 1963 GMP Regulations (Part 133.4) stated as follows: "Equipment shall be maintained in a clean and orderly manner." A similar section on equipment cleaning (211.67) was included in the 1978 cGMP regulations. Of course, the main rationale for requiring clean equipment is to prevent contamination or adulteration of drug products. Historically, FDA investigators have looked for gross insanitation due to inadequate cleaning and maintenance of equipment and/or poor dust-control systems. Also, historically speaking, the FDA was more concerned about contamination of nonpenicillin drug products with penicillins or cross-contamination of drug products with potent steroids or hormones. A number of products have been recalled over the past decade due to actual or potential penicillin cross-contamination.

One event that increased FDA awareness of the potential for cross-contamination due to inadequate procedures was the 1988 recall of a finished drug product, cholestyramine resin USP. The bulk pharmaceutical chemical used to produce the product had become contaminated

with low levels of intermediates and degradants from the production of agricultural pesticides. The FDA instituted an import alert in 1992 on a foreign bulk pharmaceutical manufacturer that manufactured potent steroid products as well as nonsteroidal products using common equipment. This firm was a multiuse bulk pharmaceutical facility. The FDA considered the potential for cross-contamination to be significant and to pose a serious health risk to the public. The firm had only recently started a cleaning validation program at the time of the inspection, and it was considered inadequate by the FDA. One of the reasons why it was considered inadequate was that the firm was only looking for evidence of the absence of the previous compound. The firm had evidence, from TLC tests on the rinse water, of the presence of residues of reaction byproducts and degradants from the previous process.

III. GENERAL REQUIREMENTS

- The FDA expects firms to have written standard operating procedures (SOPs) detailing the cleaning processes used for various pieces of equipment. If firms have one cleaning process for cleaning between different batches of the same product and use a different process for cleaning between product changes, the FDA expects the written procedures to address these different scenarios. Similarly, if firms have one process for removing water-soluble residues and another process for non-water-soluble residues, the written procedure should address both scenarios and make it clear when a given procedure is to be followed. Bulk pharmaceutical firms may decide to dedicate certain equipment for particular chemical manufacturing process steps that produce tarry or gummy residues that are difficult to remove from the equipment. Fluid-bed dryer bags are another example of equipment that is difficult to clean and is often dedicated to a specific product. Any residues from the cleaning process itself (detergents, solvents, etc.) also have to be removed from the equipment.
- The FDA expects firms to have written general procedures on how cleaning processes will be validated.

- The FDA expects the general validation procedures to address who is responsible for performing and approving the validation study, the acceptance criteria, and when revalidation will be required.
- The FDA expects firms to prepare specific written validation protocols in advance for the studies to be performed on each manufacturing system or piece of equipment which should address such issues as sampling procedures and analytical methods to be used, including the sensitivity of those methods.
- The FDA expects firms to conduct the validation studies in accordance with the protocols and to document the results of studies.
- The FDA expects a final validation report that is approved by management and states whether or not the cleaning process is valid. The data should support a conclusion that residues have been reduced to an “acceptable level”.

IV. EVALUATION OF CLEANING VALIDATION

The first step is to focus on the objective of the validation process; some companies fail to develop such objectives prior to establishing all sorts of protocols and detailed investigations. It is not unusual to see manufacturers use extensive sampling and testing programs following the cleaning process without ever really evaluating the effectiveness of the steps used to clean the equipment. Several questions need to be addressed when evaluating the cleaning process. For example, at what point does a piece of equipment or system become clean? Does it have to be scrubbed by hand? What is accomplished by hand scrubbing rather than just a solvent wash? How variable are manual cleaning processes from batch to batch and product to product? The answers to these questions are obviously important to the evaluation of the cleaning process because one must determine the overall effectiveness of the process. Answers to these questions may also identify steps that can be eliminated for more effective measures and result in resource savings for the company.

Ideally, a piece of equipment or system will have one process for cleaning; however, this will depend on the products being produced and whether the cleanup occurs between batches of the same product (as in a large campaign) or between batches of different products. When the cleaning process is used only between batches of the same product (or different lots of the same intermediate in a bulk process), the manufacturer must only meet a criterion of “visibly clean” for the equipment; such between-batch cleaning processes do not require validation.

A. EQUIPMENT DESIGN

The design of equipment, particularly in large systems that may employ semiautomatic or fully automatic clean-in-place (CIP) systems, is important. For example, a sanitary type of piping without ball valves should be used. When such ball valves are used, as is common in the bulk drug industry, the cleaning process is more difficult. When such systems are identified, it is important that operators performing cleaning operations be aware of problems and have special training in cleaning these systems and valves. The cleaning operators must have knowledge of these systems and the level of training and experience required for cleaning these systems. Also, the written and validated cleaning process must be properly identified and validated.

In larger systems, such as those employing long transfer lines or piping, flow charts and piping diagrams must be available for the identification of valves, as well as written cleaning procedures. Piping and valves should be tagged and easily identifiable by the operator performing the cleaning function. Sometimes, inadequately identified valves, both on prints and physically, have led to incorrect cleaning practices.

The documentation should be complete in regard to the cleaning processes of critical steps and should identify and control the length of time between the end of processing and each cleaning step. This is especially important for topicals, suspensions, and bulk drug operations. In such operations, the drying of residues will directly affect the efficiency of a cleaning process.

Whether or not CIP systems are used for cleaning of processing equipment, the microbiological aspects of equipment cleaning should be considered, largely through taking preventive measures rather than removing contamination once it has occurred. Manufacturers should maintain some evidence that routine cleaning and storage of equipment do not allow microbial proliferation. For example, equipment should be dried before storage, and under no circumstances should stagnant water be allowed to remain in equipment subsequent to cleaning operations.

Subsequent to the cleaning process, equipment may be subjected to sterilization or sanitization procedures when such equipment is used for sterile processing or to nonsterile processing when products may support microbial growth. While such sterilization or sanitization procedures are beyond the scope of this guide, it is important to note that control of the bioburden through adequate cleaning and storage of equipment is important to ensure that subsequent sterilization or sanitization procedures achieve the necessary level of sterility. This is also particularly important from the standpoint of the control of pyrogens in sterile processing, as equipment sterilization processes may not be adequate to achieve significant inactivation or removal of pyrogens.

B. CLEANING PROCESS, WRITTEN PROCEDURE, AND DOCUMENTATION

The detail and specificity of the procedure for the (cleaning) process being validated and the amount of documentation required to establish it are critical. Some manufacturers use general SOPs, while others use a batch record or log sheet system that requires some type of specific documentation for performing each step. Depending on the complexity of the system and cleaning process and the ability and training of the operators, the amount of documentation necessary for executing various cleaning steps or procedures will vary.

When more complex cleaning procedures are required, it is important to document the critical cleaning steps (for example, certain bulk drug synthesis processes). In this regard, it is valuable to have specific documentation on the equipment itself that includes information about who cleaned it and when; however, for relatively simple cleaning operations, merely documenting that the overall cleaning process was performed might be sufficient.

Other factors, such as history of cleaning, residue levels found after cleaning, and variability of test results, may also dictate the amount of documentation required. For example, when variable residue levels are detected following cleaning, particularly for a process that is believed to be acceptable, one must establish the effectiveness of the process and operator performance. Appropriate evaluations must be made, and when operator performance is deemed a problem more extensive documentation (guidance) and training may be required.

C. ANALYTICAL METHODS

The specificity and sensitivity of the analytical method used to detect residuals or contaminants should be well established. With advances in analytical technology, residues from the manufacturing and cleaning processes can be detected at very low levels. If levels of contamination or residual are not detected, it does not mean that no residual contaminant is present after cleaning. It only means that levels of contaminant greater than the sensitivity or detection limit of the analytical method are not present in the sample. The firm should challenge the analytical method in combination with the sampling methods used to show that contaminants can be recovered from the equipment surface and at what level (e.g., 50 or 90% recovery). This is necessary before any conclusions can be made based on the sample results. A negative test may also be the result of poor sampling technique (see below).

D. SAMPLING

Two general types of sampling have been found to be acceptable. The most desirable is the direct method of sampling the surface of the equipment, and the other method is the use of rinse solutions.

1. Direct Surface Sampling

The type of sampling material used and its impact on the test data must be identified, as the sampling material may interfere with the test; for example, the adhesive used in swabs has been found to interfere with analysis of samples. Therefore, early in the validation program, it is important to ensure that the sampling medium and solvent (used for extraction from the medium) are satisfactory and can be readily used. Advantages of direct sampling are that areas that are the most difficult to clean and which are reasonably accessible can be evaluated, leading to establishment of a level of contamination or residue per given surface area. Additionally, residues that are dried out or are insoluble can be sampled by physical removal.

2. Rinse Samples

Two advantages of using rinse samples are that a larger surface area may be sampled and inaccessible systems or ones that cannot be routinely disassembled can be sampled and evaluated. A disadvantage of rinse samples is that the residue or contaminant may not be soluble or may be physically occluded in the equipment. An analogy that can be used is a dirty pot. When evaluating the cleaning of a dirty pot, particularly one with dried-out residue, one does not look at the rinse water to see that it is clean; one looks at the pot. It is important to ensure that a direct measurement of the residue or contaminant is made for the rinse water when it is used to validate the cleaning process. For example, it is not acceptable to simply test rinse water for water quality (does it meet the compendia tests?) rather than test it for potential contaminants.

3. Routine Production In-Process Control Monitoring

Indirect testing, such as conductivity testing, may be of some value for routine monitoring once a cleaning process has been validated. This would be particularly true for bulk drug substance manufacturers whose reactors, centrifuges, and piping between such large equipment can be sampled only using rinse solution samples. Any indirect test method must have been shown to correlate with the condition of the equipment. During validation, a manufacturer should be able to provide documentation that testing the uncleaned equipment gives a not acceptable result for the indirect test.

V. ESTABLISHMENT OF LIMITS

The FDA does not generally set acceptance specifications or methods for determining whether a cleaning process is validated. It is impractical for the FDA to do so due to the wide variation in equipment and products used

throughout the bulk and finished dosage form industries. A manufacturer's rationale for the residue limits established should be logical based on the manufacturer's knowledge of the materials involved and should be practical, achievable, and verifiable. It is important to define the sensitivity of the analytical methods in order to set reasonable limits. Some limits that have been mentioned by industry representatives in the literature or in presentations include analytical detection levels (such as 10 ppm), biological activity levels (such as 1/1000 of the normal therapeutic dose), and organoleptic levels such as no visible residue.

The manner in which limits are established should be documented. Unlike finished pharmaceuticals, where the chemical identities of residuals are known (e.g., from actives, inactives, detergents), bulk processes may have partial reactants and unwanted byproducts that may never have been chemically identified. In establishing residual limits, it may not be adequate to focus only on the principal reactant, as other chemical variations may be more difficult to remove. In some circumstances, TLC screening, in addition to chemical analyses, may be needed. In a bulk process, particularly for very potent chemicals such as some steroids, the issue of byproducts must be considered if equipment is not dedicated.

VI. OTHER ISSUES

A. PLACEBO PRODUCT

In order to evaluate and validate cleaning processes, some manufacturers have processed a placebo batch in the equipment under essentially the same operating parameters used for processing product. A sample of the placebo batch is then tested for residual contamination. One cannot be sure that a contaminant is uniformly distributed throughout the system. For example, if the discharge valve or chute of a blender is contaminated, the contaminant would probably not be uniformly dispersed in the placebo; it would most likely be concentrated in the initial dis-

charge portion of the batch. Additionally, if the contaminant or residue is of a larger particle size, it may not be uniformly dispersed in the placebo. Some firms have made the assumption that a residual contaminant would wear off the equipment surface uniformly, but this is an invalid conclusion. Finally, the analytical power may be greatly reduced by dilution of the contaminate. Because of such problems, rinse and/or swab samples should be used in conjunction with the placebo method.

B. DETERGENT

If a detergent or soap is used for cleaning, evaluate the difficulty that may arise when attempting to test for residues. A common problem associated with detergent use is its composition. Many detergent suppliers will not provide a specific composition, which makes it difficult for the user to evaluate residues. As with product residues, it is important and it is expected that the manufacturer evaluate the efficiency of the cleaning process for the removal of residues. However, unlike product residues, it is expected that no (or, for ultrasensitive analytical tests, very little) detergent remains after cleaning. Detergents are not part of the manufacturing process and are only added to facilitate cleaning during the cleaning process. Thus, they should be easily removable; otherwise, a different detergent should be selected.

C. TEST UNTIL CLEAN

Evaluate the level of testing and the retest results when using this concept. Test, resample, and retest equipment or systems until an acceptable residue level is attained. For a system or equipment with a validated cleaning process, this practice of resampling should not be utilized and is acceptable only in rare cases. Constant retesting and resampling can show that the cleaning process is not validated, as these retests actually document the presence of unacceptable residue and contaminants from an ineffective cleaning process.

Part II

Over-the-Counter Product Formulations

Acetaminophen and Caffeine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Acetaminophen (fine powder)	500.00
65.00	2	Anhydrous caffeine	65.00
15.00	3	Maize starch	15.00
10.00	4	Povidone (PVP K-30)	10.00
5.00	5	Croscarmellose sodium (Ac-Di-Sol)	5.00
33.00	6	Maize starch	33.00
8.00	7	Povidone (PVP K-90)	8.00
1.00	8	Polysorbate 80 (Tween 80)	1.00
10.00	9	Microcrystalline cellulose (Avicel™ PH102)	10.00
7.00	10	Sodium starch glycolate (Primojel®)	7.00
5.00	11	Croscarmellose sodium (Ac-Di-Sol)	5.00
2.00	12	Stearic acid (fine powder)	2.00
4.00	13	Talc (fine powder)	4.00
—	14	Purified water	155.00

MANUFACTURING DIRECTIONS

Sift items 1 to 5 through a stainless steel 630- μ m sieve. Load into mixer. Mix for 5 minutes at low speed. Dissolve items 7 and 8 in 115 g of purified water (80 to 90°C) in a vessel. Prepare a slurry of item 6 in 40 g of purified water (25 to 30°C). Add the slurry to the vessel to make a translucent paste. Cool to 45 to 50°C. Add the binder (item 4) to the paste. Mix at low speed over a period of 3 minutes. Scrape sides and blades. Mix and chop at low speed for 1 to 2 minutes. Check the end point of granulation. If required, add additional purified water to obtain the end point. (The end point of granulation occurs when the wet mass consists of few or no lumps.) Unload the wet granules into stainless steel trays for drying. Dry the wet granules at 55°C for 8.0 hours. After 2.0 hours of

drying, scrape the semidried granules to break up the lumps to promote uniform drying. Check the LOD (limit: 1.5 to 2.0%). If required, dry further at 55°C for 1 hour. Grind the dried granules through a 1.25-mm sieve using a granulator at medium speed. Collect in stainless steel drums. Load the granules into blender. Sift items 9, 10, and 11 through a 500- μ m sieve using a suitable sifter, and add it to the blender. Mix for 2 minutes. Sift items 12 and 13 through a 500- μ m sieve. Add 5 to 10 g granules from bulk. Mix in. Check temperature and humidity before start of compression (recommended: relative humidity 55 to 60% at a temperature not exceeding 27°C). Compress the granules using a rotary tableting machine. Average weight of tablet is 665.00 mg.

Acetaminophen and Caffeine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Acetaminophen (crystalline)	500
50.00	2	Caffeine (Knoll)	50
90.00	3	Avicel® PH101	90
10.00	4	Kollidon® 30	10
20.00	5	Kollidon® CL	20
10.00	6	Polyethylene glycol (PEG-6000) (powder)	10

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with high compression force. Compress into 683-mg

tablets using 12-mm biplanar punches. If the flowability of the powder mixture for tableting is not high enough, some Aerosil 200 should be added.

Acetaminophen and Diphenhydramine Hydrochloride Hot Therapy Sachets

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Quantity/1000 Sachets (g)
1 650.00	1	Acetaminophen (micronized)	1 650.00
2 50.00	2	Diphenhydramine hydrochloride	2 50.00
0.90	3	FD&C Yellow Dye No. 10 lake	0.90
0.0005	4	FD&C Red Dye No. 40	0.0005
18081.10	5	Caster sugar	18081.10
200.00	6	Aspartame	200.00
250.00	7	Maize starch (dried)	250.00
180.00	8	Citric acid	180.00
38.00	9	Sodium citrate	38.00
200.00	10	Sodium chloride	200.00
240.00	11	Honey flavor (dry)	240.00
100.00	12	Lemon flavor (dry)	100.00
QS	13	Purified water	QS

MANUFACTURING DIRECTIONS

Mix items 1 and 2 well, then pass through 0.8 mm sieves. Mix items 3, 5, and 13 to make a clear solution. Add mixture of items 1 and 2 to second step mixture, and mix well. Add this mixture to item 4, and mix. Take care to

avoid lump formation. Dry in an oven and maintain a constant temperature. Sieve, and add items 6 to 12. Mix well. Make sure all the solids added are in fine powder form. Fill 20 g of powder into sachets, and seal.

Acetaminophen and Pseudoephedrine Hydrochloride Hot Therapy Sachets

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Quantity/1000 Sachets (g)
650.00	1	Acetaminophen (micronized)	650.00
2 60.00	2	Pseudoephedrine hydrochloride	260.00
0.90	3	FD&C Yellow Dye No.10 lake	0.90
18081.10	4	Caster sugar	18081.10
200.00	5	Aspartame	200.00
250.00	6	Maize starch (dried)	250.00
180.00	7	Citric acid	180.00
38.00	8	Sodium citrate	38.00
200.00	9	Sodium chloride	200.00
240.00	10	Apple flavor (dry)	240.00
100.00	11	Cinnamon flavor (dry)	100.00
QS	12	Purified water	QS

MANUFACTURING DIRECTIONS

Mix item 1 and 2 well, pass through an 0.8 mm sieve, and add to items 3 and 12, which have been mixed together. Make into a clear solution. Take care to avoid lump

formation. Dry in an oven and maintain constant moisture. Using a 500 mm sieve, add items 6 to 11. Mix well. Make sure all the solids added are in fine powder form. Fill 20 g of powder into sachets, and seal.

Acetaminophen and Diphenhydramine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
325.00	1	Acetaminophen (fine powder)	325.00
26.00	2	Diphenhydramine HCl	26.00
50.00	3	Maize starch	50.00
07.00	4	Povidone (PVP K-30)	7.00
50.00	5	Microcrystalline cellulose (Avicel™ PH101)	50.00
42.00	6	Corn starch	42.00
10.00	7	Povidone (PVP K-30)	10.00
09.50	8	Cellulose (powdered)	9.50
65.50	9	Cellulose (microcrystalline) (Avicel™ PH102)	65.50
20.00	10	Sodium starch glycolate (Primojel®)	20.00
08.00	11	Stearic acid (fine powder)	8.00
05.00	12	Talc (fine powder)	5.00
02.00	13	Magnesium stearate	2.00
	14	Purified water	180.00

MANUFACTURING DIRECTIONS

Sift items 1 to 5 through a 630- μ m stainless steel sieve. Load into mixer. Mix for 5 minutes at low speed. Dissolve item 7 in 135 g of purified water (80 to 90°C) in a vessel. Prepare a slurry of item 6 in 45 g of purified water (25 to 30°C). Add the slurry to the vessel to make a translucent paste. Cool to 45 to 50°C. Add the binder (item 4). Mix at low speed over a period of 3 minutes. Scrape sides and blades. Mix and chop at low speed for 1 to 2 minutes. Check the end point of granulation. If required, add additional purified water to obtain the end point. (The end point of granulation occurs when the wet mass consists of few or no lumps.) Unload the wet granules into stainless steel trays for drying. Dry the wet granules in an oven at 55°C for 10.0 hours. After 2.0 hours of drying, scrape the semidried granules to break up the lumps to promote uniform drying. Check the LOD (limit: 1.0 to 2.0%). If

required, dry further at 55°C for 1 hour. Grind the dried granules through a 1.25-mm sieve at medium speed. Collect in stainless steel drums. Load the granules into blender. Sift items 8, 9, and 10 through a 500- μ m sieve using a suitable sifter, and add mixture to blender. Mix for 2 minutes. Sift items 11, 12, and 13 through a 500- μ m sieve. Add 5 to 10 g of granules from bulk. Mix in polyethylene bag for 1 minute. Add to blender. Blend for 1 minute. Check temperature and humidity before start of compression (limit: temperature not exceeding 27°C; relative humidity 55 to 65%). Compress the granules using a rotary tableting machine. Compress average tablet weight of 620 mg. Disintegration time is not more than (NMT) 15 minutes; friability NMT is 1.0%. *Coating:* Use one of the HPMC aqueous formulations in the Appendix, such as Yellow Opadry.

Acetaminophen and Pseudoephedrine Hydrochloride Tablets

Bill of Materials			
Scale (mg/caplet)	Item	Material Name	Quantity/1000 Caplets (g)
325.00	1	Acetaminophen (fine powder)	325.00
31.50	2	Pseudoephedrine HCl	31.50
50.00	3	Corn starch	50.00
7.00	4	Povidone (PVP K-30)	7.00
50.00	5	Microcrystalline cellulose (Avicel™ PH101)	50.00
42.00	6	Corn starch	42.00
10.00	7	Povidone (PVP K-30)	10.00
9.50	8	Cellulose (powdered)	9.50
60.00	9	Cellulose (microcrystalline) (Avicel™ PH102)	60.00
20.00	10	Sodium starch glycolate (Primojel®)	20.00
8.00	11	Stearic acid (fine powder)	8.00
5.00	12	Talc (fine powder)	5.00
2.00	13	Magnesium stearate	2.00
—	14	Purified water	180.00

MANUFACTURING DIRECTIONS

Sift items 1 to 5 through a stainless steel 630- μ m sieve. Load into mixer. Mix for 5 minutes at low speed. Dissolve item 7 in 135 g of purified water (80 to 90°C) in a vessel. Prepare a slurry of item 6 in 45 g of purified water (25 to 30°C). Add the slurry to the vessel to make a translucent paste. Cool to 45 to 50°C. Add the binder (item 4). Mix at low speed over a period of 3 minutes. Scrape sides and blades. Mix and chop at low speed for 1 to 2 minutes. Check the end point of granulation. If required, add additional purified water to obtain the end point. (The end point of granulation occurs when the wet mass consists of few or no lumps.) Unload the wet granules into stainless steel trays for drying. Dry the wet granules in oven at 55°C for 10.0 hours. After 2.0 hours of drying, scrape the semidried granules to break up the lumps for uniform

drying. Check the LOD (limit: 1.0 to 2.0%). If required, dry further at 55°C for 1 hour. Transfer the dried granules to stainless steel drums. Grind the dried granules through a 1.25-mm sieve using granulator at medium speed. Collect in stainless steel drums. Load the granules into blender. Sift items 8, 9, and 10 through a 500- μ m sieve using a suitable sifter, and add to blender. Mix for 2 minutes. Sift items 11, 12, and 13 through a 500- μ m sieve. Add 5 to 10 g of granules. Mix in polyethylene bag for 1 minute. Add to blender. Blend for 1 minute. Unload in stainless steel drums. Compress 620 mg in 6-mm capsule-shaped punches. Coat. The formula for the coating solution is determined to obtain a weight gain of 10 mg per caplet, considering evaporation and loss during the coating operation.

Acetaminophen Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Acetaminophen, milled (Hoechst)	300.00
600.00	2	Sucrose, milled	600.00
550.00	3	Kollidon® CL-M	550.00
30.00	4	Orange flavor (FDO)	30.00
30.00	5	Strawberry flavor (FDO)	30.00
60.00	6	Kollidon® 30	60.00
QS	7	Ethanol (96%)	~425.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 5 with solution of items 6 and 7, pass through a sieve, and press with medium

compression force. Average weight of tablet is 1620 mg using a 20-mm biplanar punch. Taste is sweet, fruity, and only very slightly bitter.

Acetaminophen, Chlorpheniramine, and Pseudoephedrine Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
24.00	1	Acetaminophen (fine powder)	24.00
3.00	2	Pseudoephedrine HCl	3.00
0.44	3	Chlorpheniramine maleate (10% excess)	0.44
14.00	4	Ascorbic acid	14.00
2.40	5	Sodium hydroxide	2.40
1.00	6	Edetate disodium (sodium EDTA)	1.00
0.50	7	Saccharin sodium	0.50
2.00	8	Sodium metabisulfite (sodium disulfite)	2.00
80.00	9	Alcohol (ethanol, 95%)	80.00
100.00	10	Propylene glycol	100.00
100.00	11	Sorbitol (70% solution)	100.00
250.00	12	Glycerin (glycerol)	250.00
300.00	13	Sucrose	300.00
0.04	14	Quinoline yellow	0.04
0.25	15	Pineapple flavor	0.25
QS	16	Purified water	QS to 1 L

MANUFACTURING DIRECTIONS

Add 200.0 g of item 16 to the manufacturing vessel, and heat to 90 to 95°C. Add item 13 while mixing at slow speed at a temperature of 90 to 95°C. Mix for 1 hour at high speed. Add items 12, 10, and 11 to the manufacturing vessel while mixing at high speed. Mix for 10 minutes. Cool the temperature to 50°C while mixing at slow speed. Add 70.0 g of item 9 to the syrup solution while mixing at slow speed. Load item 1 into the manufacturing vessel while mixing at high speed. Mix for 30 minutes to obtain a clear solution. Check the clarity of the solution. Flush the solution with nitrogen gas for 5 minutes at 1 bar. Add items 6, 8, 4, and 2 to the manufacturing vessel while mixing at slow speed. Dissolve item 3 in 2.0 g of item 16 (25°C), and check that the solution is complete. Add the solution to the manufacturing vessel while mixing at slow speed. Dissolve item 15 in 10.0 g of item 9 in a stainless steel container, and add to the manufacturing vessel while

mixing at slow speed. Dissolve items 5 and 7 in 20.0 g of item 16 (25°C), and add to the manufacturing vessel while mixing at slow speed. Dissolve item 14 in 2.0 g of item 16 (25°C). Transfer the color solution to the manufacturing vessel while mixing at slow speed. Rinse the container of color solution with 2.0 g of item 16 (25°C), then transfer the rinsing to the manufacturing vessel, and mix for 5 minutes at high speed. Bring the volume up to 1.0 L with item 16, and finally mix for 15 to 20 minutes at high speed. Check and record the pH (limit: 5.1 to 5.2). If required, adjust pH with 10% citric acid or 10% sodium citrate solution. Assemble the filter press with 13.1 T 1000 12 sheets (K 800 14 sheets). Use changeover plate. Wash the filters using purified water (25°C) by passing through filters at 0.2 bar; discard the washings. Filter the syrup at 1.5 bar. Recirculate about 20 to 30 mL syrup. Connect the hose to the manufacturing vessel, and transfer the filtered syrup to the storage vessel.

Acetaminophen, Chlorpheniramine Maleate, and Pseudoephedrine Caplets

Bill of Materials			
Scale (mg/caplet)	Item	Material Name	Quantity/1000 Caplets (g)
325.00	1	Acetaminophen (fine powder)	325.00
31.50	2	Pseudoephedrine HCl	31.50
2.10	3	Chlorpheniramine maleate	2.10
50.00	4	Corn starch	50.00
7.00	5	Povidone (PVP K-30)	7.00
50.00	6	Cellulose (microcrystalline) (Avicel™ PH101)	50.00
42.00	7	Corn starch	42.00
10.00	8	Povidone (PVP K-30)	10.00
9.50	9	Powdered cellulose	9.50
77.90	10	Cellulose (microcrystalline) (Avicel™ PH102)	77.90
20.00	11	Sodium starch glycolate (Primojel®)	20.00
8.00	12	Stearic acid (fine powder)	8.00
5.00	13	Talc (fine powder)	5.00
2.00	14	Magnesium stearate	2.00
—	15	Purified water	180.00

MANUFACTURING DIRECTIONS

Sift items 1 to 6 through a 630- μ m stainless steel sieve. Load into mixer. Mix for 5 minutes at low speed. Dissolve item 8 in 135 g of item 15 (80 to 90°C) in a vessel. Prepare a slurry of item 7 in 45 g of item 15 (25 to 30°C). Add the slurry to the vessel to make a translucent paste. Cool to 45 to 50°C. Add the binder (item 5) to step above. Mix at low speed over a period of 3 minutes. Scrape sides and blades. Mix and chop at low speed for 1 for 2 minutes. Check the end point of granulation. If required, add additional item 15 to obtain the end point. (The end point of granulation occurs when the wet mass consists of few or no lumps.) Unload the wet granules in stainless steel trays for drying. Dry the wet granules at 55°C for 10.0 hours. After 2.0 hours of drying, scrape the semidried granules to break up the lumps to promote uniform drying. Check the LOD (limit: 1.0 to 2.0%). If required, dry further at

55°C for 1 hour. Grind the dried granules through a 1.25-mm sieve at medium speed. Collect in stainless steel drums. Load the granules into blender. Sift items 9, 10, and 11 through a 500- μ m sieve using suitable sifter and add mixture to blender. Mix for 2 minutes. Sift items 12, 13, and 14 through a 500- μ m sieve. Add 5 to 10 g of granules from bulk. Mix in polyethylene bag for 1 minute. Add to blender. Blend for 1 minute. Check temperature and humidity before start of compression; temperature should not exceed 27°C, and recommended relative humidity is 55 to 65%. Compress the granules using rotary tableting machine. Tablet weight is 640 mg. *Coating:* Select an appropriate coating such as Opadry HPMC. The formula for the coating solution is determined to obtain a weight gain of 10 mg per caplet, considering evaporation and loss during coating operation.

Acetaminophen, Dextromethorphan, and Pseudoephedrine Caplets

Bill of Materials			
Scale (mg/caplet)	Item	Material Name	Quantity/1000 Caplets (g)
325.00	1	Acetaminophen (fine powder)	325.00
31.50	2	Pseudoephedrine HCl	31.50
15.50	3	Dextromethorphan HBr	15.50
50.00	4	Corn starch	50.00
7.00	5	Povidone (PVP K-30)	7.00
50.00	6	Cellulose (microcrystalline) (Avicel™ PH101)	50.00
42.00	7	Corn starch	42.00
10.00	8	Povidone (PVP K-30)	10.00
9.50	9	Cellulose (powdered)	9.50
64.50	10	Cellulose (microcrystalline) (Avicel™ PH102)	64.50
20.00	11	Sodium starch glycolate (Primojel®)	20.00
8.00	12	Stearic acid (fine powder)	8.00
5.00	13	Talc (fine powder)	5.00
2.00	14	Magnesium stearate	2.00
—	15	Purified water	180.00

MANUFACTURING DIRECTIONS

Follow manufacturing directions provided for acetaminophen, Chlorpheniramine, and pseudoephedrine Caplets.

Acetaminophen, Doxylamine, and Caffeine Effervescent Granules

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Quantity/1000 Sachets (g)
500.00	1	Acetaminophen (powder)	500.00
5.00	2	Doxylamine succinate	5.00
33.00	3	Caffeine (Knoll)	33.00
391.00	4	Tartaric acid	391.00
417.00	5	Sodium hydrogen carbonate	417.00
6.00	6	Kollidon® 30	6.00
—	7	Isopropanol (or ethanol)	QS
30.00	8	Sodium citrate	30.00
707.00	9	Sugar	707.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 5 with solution of items 6 and 7, dry at 60°C under vacuum conditions, through 0.8 mm sieve and mix with items 8 and 9. Fill 2.1 g in

sachets at maximum relative atmospheric humidity of 30%. Granules are free flowing. If the solvent isopropanol is replaced by water, the granulation should be done in a fluidized bed.

Acetaminophen Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
739.00	1	Propylene glycol	739.00
90.00	2	Acetaminophen	90.00
17.50	3	Saccharin sodium	17.50
8.75	4	Sodium chloride	8.75
0.05	5	FD&C Red Dye No. 40 ^a	0.05
2.50	6	Purified water, USP	2.50
2.00	7	Wild cherry artificial flavor	2.00
65.00	8	Alcohol (ethanol; 190 proof; non-beverage), USP	65.00
QS	9	Deionized purified water, USP	QS to 1 L

^a Check for local regulatory allowance to use red dyes.

MANUFACTURING DIRECTIONS

Caution: Ensure that solution in tank never exceeds 65°C. Add 739 g of propylene glycol to jacketed mixing tank, and start heating with slow mixing. Dissolve dye in 2.5 mL of purified water, and add to tank while mixing. Rinse container with small amount of purified water and add to tank. While mixing, add acetaminophen, saccharin

sodium, and sodium chloride. Hold at 60 to 65°C with continued moderate mixing until all are in solution. Force cool to less than 30°C with slow mixing. Blend flavor with alcohol, and add to tank with slow mixing. Add purified water with mixing QS to make 1 L. Mix well with moderate agitation until uniform. Filter through an 8-µm Milipore membrane (or equivalent).

Acetaminophen Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Acetaminophen ¹ (powder < 300 µm)	500.00
500.00	2	Sodium bicarbonate	500.00
430.00	3	Tartaric acid (powder)	430.00
200.00	4	Dextrose	200.00
QS	5	Flavoring	QS
20.00	6	Kollidon® 30	20.00
—	7	Isopropanol	100.00 mL
60.00	8	PEG-6000 (powder)	60.00

MANUFACTURING DIRECTIONS

Granulate the mixture of items 1 to 5 with solution of items 6 and 7, pass through an 0.8-mm sieve, add item 8,

mix, and press to tablets (average weight, 1700 mg; 16-mm-diameter biplanar tablet).

Acetaminophen, Ibuprofen, and Orphenadine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Acetaminophen (powder < 300 µm)	250.00
200.00	2	Ibuprofen	200.00
100.00	3	Orphenadine hydrochloride	100.00
200.00	4	Ludipress®	200.00
5.00	5	Magnesium stearate	5.00
5.00	6	Aerosil® 200	5.00

MANUFACTURING DIRECTIONS

Pass all components through a 0.5-mm sieve, mix, and press with high compression force. Tablet weight is 761 mg for a 12-mm biplanar tablet.

Acetaminophen Instant Granules

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
166.66	1	Acetaminophen (fine powder)	166.66
426.64	2	Sucrose (fine powder)	426.64
300.00	3	Kollidon® CL-M	300.00
23.33	4	Aspartame	23.33
16.66	5	Orange flavor	16.66
16.66	6	Strawberry flavor	16.66
40.00	7	Kollidon® 30	40.00
250.00	8	Ethanol (96%)	250.00

MANUFACTURING DIRECTIONS

Granulate items 1 to 6 with solution made from items 10 and 11, and pass through an 0.8-mm sieve. Fill 1.5 or 3.0 g in sachets (for 250- or 500-mg strength, respectively). The

free-flowing granules disperse very well in cold water. Suspend 1.5 or 3.0 g of the granules (= 250 mg or 500 mg acetaminophen) in a glass of water.

Acetaminophen Instant Granules

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
192.30	1	Acetaminophen (fine powder)	192.30
500.00	3	Sorbitol (instant) (Merck)	500.00
192.30	4	Kollidon® CL-M	192.30
27.00	5	Aspartame	27.00
19.23	6	Orange flavor	19.23
19.23	7	Strawberry flavor	19.23
11.53	8	Sodium citrate	11.53
11.53	9	Citric acid	11.53
30.76	10	Kollidon® 90 F	30.76
192.30	11	Ethanol (96%)	192.30

MANUFACTURING DIRECTIONS

Granulate items 1 to 9 with solution made from items 10 and 11, and pass through an 0.8-mm sieve. Fill 1.3 or 2.6 g in sachets (for 250- or 500-mg strength, respectively). The

free-flowing granules disperse very well in cold water. Suspend 1.2 or 2.6 g of the granules (= 250 mg or 500 mg acetaminophen) in a glass of water.

Acetaminophen Instant Granules

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Quantity/1000 Sachets (g)
500.00	1	Acetaminophen fine powder	500.00
1300.00	2	Sorbitol instant (Merck)	1300.00
500.00	3	Lutrol F 127	500.00
30.00	4	Citric acid (powder)	30.00
30.00	5	Sodium citrate	30.00
80.00	6	Kollidon® 90 F	80.00
500.00	7	Ethanol (96%)	500.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 5 in solution of item 6 in item 7. Fill 2.44 g in sachets (= 500 mg acetaminophen). The free-flowing granules disperse very well in cold water.

The taste of the suspension is only slightly bitter (2.44 g in a glass of water). No sedimentation can be observed for some minutes.

Acetaminophen, Norephedrine, and Phenyltoloxamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Acetaminophen (crystalline) (Merck)	300.00
25.00	2	Norephedrine hydrochloride (Knoll)	25.00
22.00	3	Phenyltoloxamine	22.00
200.00	4	Corn starch	200.00
25.00	5	Kollidon® 30	25.00
—	6	Ethanol (96%)	QS
25.00	7	Kollidon® CL	25.00
5.00	8	Magnesium stearate	5.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 5 with solution of items 5 and 6, dry, pass through an 0.8-mm sieve, add items 7

and 8, and press with high compression force. Tablet weight is 601 mg for 12-mm biplanar tablet.

Acetaminophen Oral Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Quantity/L (g)
250.00	1	Acetaminophen (micronized) (2.0% excess)	51.00
2500.00	2	Sucrose	500.00
5.00	3	Methyl paraben	1.00
1.50	4	Propyl paraben	0.30
0.30	5	Sodium citrate	0.06
35.00	6	Glycerin (glycerol)	7.00
400.00	7	Glycerin (glycerol)	80.00
2000.00	8	Sorbitol (70%)	400.00
10.00	9	Xanthan gum (Keltrol® F)	2.00
0.50	10	Dye	0.10
22.50	11	Flavor	4.50
3.50	12	Strawberry flavor	0.70
—	13	Purified water	QS to 1 L

MANUFACTURING DIRECTIONS

Acetaminophen dispersion should be uniformly mixed. If acetaminophen dispersion is either added to hot syrup base or homogenized for a long time, flocculation may appear. While handling the syrup or mucilage or drug dispersion, the handling loss should not be more than 1%. If it exceeds 1%, a poor suspension may result. Add 180 g of purified water to the mixer, and heat to 90°C. Dissolve item 3 and item 4 while mixing. Add and dissolve item 2 while mixing. Cool down to about 50 to 55°C. Add and dissolve item 5 while mixing. Filter the syrup through T-1500 filters washed with purified water. Collect the syrup in a clean stainless steel tank. Disperse item 9 in item 6 in a separate stainless steel container. Add 40 g of hot purified water (90°C) at once while mixing. Mix for 20 minutes to make a homogeneous smooth mucilage. Mix item 7 in 10 g of purified water (25°C) in a separate stainless steel container. Add item 1 while mixing with stirrer. Mix for 25 minutes to make uniform suspension. Add sugar syrup

and mucilage to the mixer. Rinse the container of mucilage with 15 g of purified water, and add the rinsings to the mixer. Cool to 25°C while mixing. Add item 1 dispersion to the mixer. Rinse the container of dispersion with 15 g of purified water, and add rinsings to the mixer. Check the suspension for uniformity of dispersion. Mix for additional 5 minutes at 18 rpm and a vacuum of 0.5 bar, if required. Add item 8 to the mixer, and mix for 10 minutes. Dissolve item 10 in 7 g of purified water, and add to the mixer. Disperse item 11 in 7 g of purified water, and add to the mixer. Add item 12 to the mixer. Add cold purified water (25°C) to bring the volume up to 1.0 L. Homogenize for 5 minutes at low speed under a vacuum of 0.5 bar, 18 rpm, and temperature of 25°C. Check the dispersion for uniformity. Check the pH. Limit 5.7 ± 0.5 at 25°C. If required, adjust the pH with a 20% solution of citric acid or sodium citrate. Transfer the suspension through a 630- μ m sieve to the stainless steel storage tank, after mixing for 5 minutes at 18 to 20 rpm at room temperature.

Acetaminophen, Phenylpropanolamine, Dextromethorphan, and Chlorpheniramine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Acetaminophen	200.00
12.50	2	Phenylpropanolamine hydrochloride (10% excess)	13.75
10.00	3	Dextromethorphan hydrobromide (10% excess)	11.00
1.00	4	Chlorpheniramine maleate (10% excess)	1.10
64.65	5	Cellulose (microcrystalline) (Avicel™ PH101)	121.72
28.00	6	Sodium starch glycolate (pH 5.5–7.5)	28.00
17.00	7	Povidone (PVP K-29–32)	17.5
—	8	Distilled purified water	~80.0 mL
2.00	9	Magnesium stearate	2.00
125.00	10	Acetaminophen	125.00
50.00	11	Ascorbic acid; use item 12	—
56.25	12	Sodium ascorbate (special grade) (20% excess)	67.50
24.00	13	Sodium starch glycolate (pH 5.5–7.5)	24.00
15.00	14	Povidone (PVP K-29–32)	~15.00
—	15	Alcohol SD 3A (200 proof)	75.0 mL

MANUFACTURING DIRECTIONS

Dissolve the chlorpheniramine and Povidone (item 7) in the purified water. Pass the phenylpropanolamine, dextromethorphan, and an equal portion of Avicel (item 5) through a 790- μ m screen to break up any agglomerates. Blend the screened items in a suitable mixer for 5 minutes. Load the acetaminophen (item 1), sodium starch glycolate (item 6), remaining Avicel (item 5), and blended items from previous step into a suitable planetary mixer. Blend for 10 minutes. Granulate the blend from the solution above. Add the gran-

ulating solution in three equal portions, massing for 5 minutes after each addition. Pass the wet mass through a 4.2-mm screen onto paper-lined trays. Dry at 50°C until the granule LOD is 1 to 1.5%. Pass the dried granules through an oscillating granulator fitted with a 790- μ m screen. Load the dried granules into a suitable blender. Pass the magnesium stearate through a 600- μ m screen, and add to the blender. Blend for 5 minutes. Compress to the following specifications: tablet weight of 291.0 mg, and tablet thickness of 4.20 to 4.40 mm.

Acetaminophen, Propoxyphenazone, and Caffeine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Acetaminophen powder	250.00
150.00	2	Propoxyphenazone (isopropyl antipyrine)	150.00
50.00	3	Anhydrous caffeine	50.00
120.00	4	Avicel™ PH102	120.00
5.00	5	Pharmacoat® 603	5.00
3.25	6	Magnesium stearate	3.25
9.75	7	Talcum	9.75
1.30	8	Silicic acid	1.30
7.00	9	Methocel E-15	7.00
32.50	10	Esmaspreng fine	32.50
21.20	11	Maize starch	21.20
—	12	Water purified	QS

MANUFACTURING DIRECTIONS

Place into a suitable vessel 5.00 g of Pharmacoat and 74.00 g of purified water ; stir until homogeneous aqueous mucilage is obtained. Mix in another vessel 250 g acetaminophen powder and 17.50 g Esmaspreng fine; add the above granulating solution, and knead for approximately 10 minutes until an evenly moist mass of soft lumps is obtained. Granulate by means of centrifugal granulator with 10-mm screen; dry the moist granulate overnight on trays in drying oven at 45°C (relative humidity of 20 to 30%). Crush the dried cake through an oscillator with a 1.5-mm perforated plate. In a suitable container, add 65 g deionized water and 7.0 g methocel. Stir until a homogeneous aqueous mucilage is obtained. Mix into another vessel 150 g isopropyl antipyrine, 50 g caffeine, 15 g Esmespreng fine, and 5.0 g maize starch. Pass through a centrifugal granulator with 1.0-mm screen;

place mixture into another vessel, and knead for approximately 10 minutes until an evenly moist mass of small lumps is obtained. Granulate through centrifugal granulator with 10-mm perforated screen. Dry moist granulate overnight on trays in drying oven at 45°C (relative humidity of 10 to 20%). Crush the dried granules through oscillator with a 1.5-mm perforated plate; store in airtight container. Mix into a tumbling mixer 4.875 g talc, 1.625 g magnesium stearate, 0.65 kg silicic acid, and 60.00 g Avicel PH102. Pass through a 0.5-mm round sieve, and load acetaminophen granulate and isopropyl antipyrine/caffeine granulate; add premixture of talc into blender. Mix the mixture well for 30 minutes (relative humidity of 30 to 35%). Store mix in airtight container. Compress 650-mg tablet to 12.8 to 13.2 mm; hardness, 6 to 20; disintegration time, 5 minutes.

Acetaminophen, Pseudoephedrine Hydrochloride, and Chlorpheniramine Hot Therapy Sachet

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Quantity/1000 Sachets (g)
650.00	1	Acetaminophen (micronized)	650.00
60.00	2	Pseudoephedrine hydrochloride	60.00
4.00	3	Chlorpheniramine maleate	4.00
1.20	4	Dispersed orange	1.20
18081.10	5	Caster sugar	18081.10
200.00	6	Aspartame	200.00
250.00	7	Maize starch (dried)	250.00
180.00	8	Citric acid	180.00
38.00	9	Sodium citrate	38.00
200.00	10	Sodium chloride	200.00
400.00	11	Blood orange flavor (dry)	400.00
QS	12	Purified water	QS

MANUFACTURING DIRECTIONS

See manufacturing directions for acetaminophen and pseudoephedrine hydrochloride hot therapy sachets.

Acetaminophen Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Quantity/1000 Suppositories (g)
80.00	1	Acetaminophen (micronized)	80.00
836.80	2	Hard fat (Suppocire AM)	836.80
3.20	3	Sorbitan monostearate (Crill-3)	3.20

MANUFACTURING DIRECTIONS

Fill weight is 920 mg per suppository. The molten suppository mass must be stirred throughout the storage period and during manufacturing and filling to avoid sedimentation of the active drug. Load items 2 and 3 into the fat melting vessel and heat to $50 \pm 3^{\circ}\text{C}$. Transfer the molten mass to a mixer through filter sieves. Set the temperature at $45 \pm 2^{\circ}\text{C}$. Load item 1 into the mixer containing

molten item 2. Carefully mix the powder with molten item 2 for 20 minutes at 10 rpm, at a temperature of $45 \pm 2^{\circ}\text{C}$, and at a vacuum of 0.4 to 0.5 bar, then homogenize for 10 minutes at low speed. Continue mixing at 10 rpm. Heat the storage vessel, and set the temperature at $45 \pm 2^{\circ}\text{C}$. Transfer the molten mass from the mixer to the storage vessel. Hold the mass at $45 \pm 2^{\circ}\text{C}$, with continuous mixing at low speed.

Acetaminophen Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Quantity/1000 Suppositories (g)
125.00	1	Acetaminophen (micronized) (5% excess)	131.25
785.54	2	Hard fat (Suppocire AM)	785.54
3.21	3	Sorbitan monostearate (Crill-3)	3.21

MANUFACTURING DIRECTIONS

Fill weight is 920 mg per suppository; see previous entry for manufacturing directions.

Acetaminophen Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Quantity/1000 Suppositories (g)
250.00	1	Acetaminophen (micronized)	250.00
1140.00	2	Hard fat (Suppocire AM)	1140.00

MANUFACTURING DIRECTIONS

Fill weight is 1390 mg per suppository; see previous entry for manufacturing directions.

Acetaminophen Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Quantity/1000 Suppositories (g)
150.00	1	Acetaminophen (fine powder), excess	150.00
20.00	2	Aerosil® 200	20.00
1.290.00	3	Lutrol E 1500	1.290.00
554.00	4	Lutrol E 4000	554.00

MANUFACTURING DIRECTIONS

Melt the mixture of items 1 and 2 in a mixture of items 3 and 4. Fill the molten mass in suppository molds. Average weight is 2.00 g.

Acetaminophen Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Quantity/1000 Suppositories (g)
500.00	1	Acetaminophen (fine powder)	500.00
100.00	2	Lutrol E 400	100.00
600.00	3	Lutrol E 1500	600.00
800.00	4	Lutrol E 4000	800.00

MANUFACTURING DIRECTIONS

Fill weight is 2.09; melt items 2 through 4 and add and dispense item 1. Fill the molten mass in suppository molds.

Acetaminophen Suspension

Bill of Materials			
Scale (mg/10 mL)	Item	Material Name	Quantity/L (g)
500.00	1	Acetaminophen (powder)	50.00
50.00	2	Citric acid (powder)	5.00
50.00	3	Sodium citrate	5.00
500.00	4	Kollidon® CL-M	50.00
10.00	5	Orange flavor	1.00
3000.00	6	Dextrose	300.00
QS	7	Water	589.00

MANUFACTURING DIRECTIONS

Prepare the solution of dextrose in water, and add the other solid ingredients with stirring in the following sequence: citric acid, sodium citrate, orange flavor, Kollidon CL-M, and acetaminophen. A white, homogeneous suspension is

obtained that is a practically tasteless, stable suspension showing almost no sedimentation over 24 hours and good redispersibility (easily homogenized by shaking two to three times).

Acetaminophen Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
569.00	1	Sucrose (granulated sugar), NF	560.00
2.00	2	Sodium citrate (dihydrate powder), USP	2.00
1.00	3	Citric acid (anhydrous powder), USP	1.00
1.00	4	Saccharin sodium (powder), USP	1.00
1.00	5	Sodium chloride (powder), USP	1.00
204.00	6	Propylene Glycol, USP	204.00
35.00	7	Acetaminophen, USP	35.00
77.11	8	Alcohol (ethanol; 190 proof), USP	77.112
0.12	9	Cherry flavor (artificial), N59456/A	0.12
0.12	10	FD&C Red Dye No. 40	0.10
QS	11	Deionized purified water, USP	400.00
—	12	HyFlo filter aid	QS

MANUFACTURING DIRECTIONS

Add 300 ml of purified water to a jacketed stainless steel mixing tank. Start heating. Add sugar with mixing. Heat to 60 to 65°C, and hold. Mix for complete solution. Add, while mixing, sodium citrate, citric acid, saccharine sodium, and sodium chloride. Mix for complete solution. Add propylene glycol with mixing. Add acetaminophen powder with moderate mixing. Continue mixing at 60 to 65°C for complete solution. Force cool to 25 to 30°C with slow mixing. Blend cherry flavor with approximately twice its volume of alcohol, and add with mixing. Rinse

the container with several portions of alcohol and add. Mix until uniform. Dissolve red dye in approximately 4.0 g of slightly warmed (50 to 60°C) purified water, and add with mixing. Rinse the container twice with approximately 1.5 g purified water and add. Mix until uniform. Adjust volume to 1 L with purified water. Mix well. Add a small amount of HyFlo filter aid to the mixing tank, and continue to mix slowly while filtering. Filter through press until sparkling clear. Use clarifying pad backed by lint-free filter paper.

Acetaminophen Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
50.00	1	Acetaminophen (Merck)	50.00
50.00	2	Sorbitol (crystalline)	50.00
40.00	3	Cyclamate sodium	40.00
1.00	4	Strawberry flavor	1.00
200.00	5	Kollidon® 25	200.00
150.00	6	Glycerol	150.00
200.00	7	1,2-Propylene glycol	200.00
310.00	8	Water	310.00

MANUFACTURING DIRECTIONS

First dissolve Kollidon 25 and then the other solid components in the solvent mixture of glycerol, propylene glycol, and water. The clear solution has a slightly bitter taste. The solution remains clear for more than 1 week at 6°C

and for more than 3 months at 25 and 40°C. The color of the solution changes only a little during 3 months at 25 and 40°C. To prevent discoloration during storage, 0.2 to 0.5% of cysteine could be added as antioxidant.

Acetaminophen Syrup for Children

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
25.00	1	Acetaminophen (crystalline)	25.00
300.00	2	Kollidon® 25 or Kollidon® 30	300.00
60.00	3	Glycerol	600.00
40.00	4	Sodium cyclamate	40.00
QS	5	Orange flavor	< 01.0
QS	6	Raspberry flavor	2.00
QS	7	Water	575.00

MANUFACTURING DIRECTIONS

Dissolve Kollidon in water, add acetaminophen and cyclamate, heat to 50°C, and stir to obtain a clear solution.

Dissolve the flavors, and mix with glycerol. The obtained syrup is a viscous, clear, sweet, and only slightly bitter liquid.

Acetaminophen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Acetaminophen (fine powder)	500.00
44.15	2	Maize starch	44.15
0.84	3	Potassium sorbate	0.84
18.00	4	Povidone (PVP K-30)	18.00
4.00	5	Aerosil® 200	4.00
12.00	6	Gelatin (powder)	12.00
4.00	7	Glycerol	4.00
30.00	8	Cellulose (powder)	30.00
12.00	9	Primojel®	12.00
8.00	10	Stearic acid (fine powder)	8.00
2.00	11	Magnesium stearate	2.00
5.00	12	Talc (fine powder)	5.00
QS	13	Purified water	QS

MANUFACTURING DIRECTIONS

Binder solution: Prepare in several batches. Add items 3 to 5 with about 50% quantity of water, dissolve item 1 in water, add item 4, and dissolve at medium speed. Avoid foaming. Add item 5, and mix for 3 minutes. Dissolve item 6 in 70 to 80°C purified water, and mix until clear. Avoid foaming. Add item 7, and mix gently; add to mixture from previous step. Mix items 1 and 2 for 5 minutes. Add binding solution, and mix at slow speed until granules form; add extra water if necessary. Dry in fluid-bed dryer at 55°C for 30 minutes; after 15 minutes, scrape granules

to break up lumps to promote uniform drying. Dry to 1 to 1.5% LOD. Grind through a 3.0-mm sieve and then through a 1.0-mm sieve; load into double-cone blender. Pass cellulose powder, Primojel, and stearic acid through a 500-µm sieve; bag-mix magnesium stearate and fine talc powder, and pass through a 250-µm sieve; add portion of granules from the bulk to the bag, and mix for 1 minute. Add both of these parts to the granules. Compress 17.6 × 7.2-mm caplet punches to 10- to 14-kp hardness and 5.8- to 6.0-mm thickness.

Acetaminophen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Acetaminophen (crystalline)	500.00
137.00	2	Avicel™ PH102	137.00
35.00	3	Kollidon® VA 64	35.00
21.00	4	Kollidon® CL	21.00
3.00	5	Magnesium stearate	3.00
4.00	6	Aerosil® 200	4.00

MANUFACTURING DIRECTIONS

Pass the lubricant through a 200-mm sieve, mix all other components, pass through 0.8-mm sieve and add the

lubricant, and press with a high compression force of 25 to 30 KN. Fill 699 mg.

Acetaminophen Tablets

Bill of Materials			
Scale (g/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500	1	Acetaminophen (crystalline)	500
150	2	Avicel™ PH102	150
20	3	Kollidon® VA 64	20
15	4	Kollidon® CL	15
15	5	PEG-6000 (powder)	15
2	6	Aerosil® 200	2

MANUFACTURING DIRECTIONS

Pass the lubricant through a 200- μ m sieve, mix all other components, pass through an 0.8-mm sieve, add the lubricant, and press with a high compression force of 25 to 30 kN. Weight should be 703 mg.

Acetaminophen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Acetaminophen (powder)	500.00
30.00	2	Dicalcium phosphate	30.00
12.00	3	Kollidon® CL	12.00
20.00	4	Kollidon® VA 64	20.00
10.00	5	Kollidon® 90 F	10.00
—	6	Ethanol (96%)	70 mL (max.)
12.00	7	Kollidon® CL	12.00
10.00	8	Polyethylene glycol (powder)	10.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 4 with solution of item 5 and 6. Dry, sieve, and mix with items 7 and 8. Press with high compression force of 25 to 30 kN. Tablet weight is 587 mg for an 11-mm biconvex tablet.

Acetaminophen Tablets for Children

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
210.00	1	Acetaminophen (Merck)	210.00
168.00	2	Avicel™ PH101	168.00
13.00	3	Kollidon® VA 64	13.00
6.00	4	Kollidon® CL	6.00
2.00	5	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with medium compression force. Tablet weight is 401 mg for a 12-mm biplanar tablet.

Acetylcysteine Sachets

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Quantity/1000 Sachets (g)
66.66	1	Acetylcysteine BP (200 mg/sachet)	66.66
914.16	2	Sugar (18 to 60 mesh)	914.16
3.33	3	Saccharin sodium	3.33
0.66	4	Silicon dioxide (colloidal)	0.66
0.16	5	FD&C Yellow Dye No. 6	0.16
QS	6	Mandarin flavor (e.g., Naarden)	~13.0 mL

MANUFACTURING DIRECTIONS

Load the acetylcysteine and half the amount of sugar and saccharin sodium into a suitable blender, and premix for 30 minutes. Sift the premix through a 0.8 mm screen. Load again into the blender. Add the remaining amount of sugar and colloidal silicon dioxide, and blend until uniform (typically, this is achieved on the PK processor by heating the envelope to 40°C and mixing until the product cools to 30 to 35°C). Dissolve the dye in 13 mL of distilled water. Continue mixing the blended powders, and slowly add the solution from step above. When addition of the solution is complete, continue massing until the granulation is evenly wetted and colored. If necessary, complete massing

by adding additional quantities of distilled water (in approximately 1-mL increments). Verify that massing is adequate, and note the total quantity of added water. Record the total quantity of water added. Do not overmass. Spread the wet granules on trays, and dry at 50°C until LOD is NMT 1% (3 hours at 60°C at 5 mmHg). Allow the granules to cool, then sift on an oscillating granulator fitted with 1.18-mm aperture screen. Load the granules from step above into a suitable blender, add the flavor, and blend until uniform (15 minutes), passing it through a 1.18-mm screen if necessary. Fill into suitable approved sachets at a theoretical fill weight of 3.0 g per sachet.

Acetylsalicylic Acid, Acetaminophen, and Caffeine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Acetylsalicylic acid (crystalline)	250.00
250.00	2	Acetaminophen (crystalline)	250.00
50.00	3	Caffeine	50.00
50.00	4	Kollidon® 90 F	50.00
—	5	Isopropanol	QS
5.00	6	Magnesium stearate	5.00
16.00	7	Kollidon® CL	16.00

MANUFACTURING DIRECTIONS

Granulate items 1 to 3 with solution of items 4 and 5; dry and sieve through an 0.8-mm screen. Add items 5 and 6,

and press with low compression force (hardness 45 N); 12-mm biplanar tablet has an average weight of 670 mg.

Acetylsalicylic Acid, Acetaminophen, and Caffeine Tablets (Direct Compression)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Acetylsalicylic acid (crystalline)	400.00
100.00	2	Acetaminophen (crystalline)	100.00
30.00	3	Caffeine	30.00
100.00	4	Ludipress®	100.00
20.00	5	Kollidon® CL	20.00
30.00	6	PEG-6000 (powder)	30.00
5.00	7	Stearic acid	5.00

MANUFACTURING DIRECTIONS

Mix all components, pass through a 0.8-mm sieve, and press with compression force of 116 N; 12-mm biplanar tablet has an average weight of 683 mg.

Acetylsalicylic Acid and Acetaminophen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Acetylsalicylic acid (crystalline)	250.00
250.00	2	Acetaminophen (crystalline)	250.00
60.00	3	Avicel™ PH101	60.00
15.00	4	Kollidon® 30 (or Kollidon® VA 64)	15.00
25.00	5	Kollidon® CL	25.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with medium compression force. Tablet weight is 605 mg for a 12-mm biplanar tablet.

Acetylsalicylic Acid and Acetaminophen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Acetylsalicylic acid (40 mesh)	250.00
250.00	2	Acetaminophen (40 mesh)	250.00
15.00	3	Avicel™ PH102	15.00
7.20	4	Croscarmellose sodium (Ac-Di-Sol)	7.20
7.20	5	Stearic acid	7.20
4.00	6	Fumed silica	4.00

MANUFACTURING DIRECTIONS

Screen all ingredients through a 0.8-mm sieve. Blend all ingredients in a V-blender, and mix for 10 minutes. Compress to 670-mg tablet weight using appropriate tooling.

Acetylsalicylic Acid and Ascorbic Acid Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
325.00	1	Acetylsalicylic acid (crystalline) (Merck)	325.00
250.00	2	Ascorbic acid (powder) (BASF)	250.00
120.00	3	Sorbitol (crystalline)	120.00
40.00	4	Avicel™ PH101	40.00
25.00	5	Kollidon® VA 64	25.00
20.00	6	Kollidon® CL	20.00
2.00	7	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with medium to high compression force (hardness 92N); 12-mm biplanar tablet has an average weight of 790 mg.

Acetylsalicylic Acid and Ascorbic Acid Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
325.00	1	Acetylsalicylic acid (crystalline) (Merck)	325.00
250.00	2	Ascorbic acid (powder) (BASF)	250.00
100.00	4	Avicel™ PH101	100.00
12.00	5	Kollidon® VA 64	12.00
30.00	6	Kollidon® CL	30.00
3.00	7	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with medium to high compression force (hardness 100 N); 12-mm biplanar tablet has an average weight of 726 mg.

Acetylsalicylic Acid Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Quantity/1000 Suppositories (g)
100.00	1	Acetylsalicylic acid	100.00
400.00	2	Suppocire AM	400.00

MANUFACTURING DIRECTIONS

Heat item 2 to 50°C. Allow to cool to 40°C, and add item 1 while stirring with a turbine mixer. Cool molds to 0 to

–5°C. Continue mixing and cooling, and pour into molds at 35°C. Remove suppositories from molds after 7 minutes. Fill to appropriate weight for strength desired.

Acetylsalicylic Acid Tablets, Buffered

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Acetylsalicylic acid (40 mesh)	400.00
40.00	2	Magnesium hydroxide	40.00
40.00	3	Aluminum hydroxide	40.00
135.00	4	Cellulose (microcrystalline) (Avicel™ PH101)	135.00
15.30	5	Stearic acid	15.30
15.30	6	Croscarmellose sodium (Ac-D-Sol)	15.30
18.50	7	Hydroxy coatings	18.50

MANUFACTURING DIRECTIONS

Screen all ingredients except the item 7 through a 40-mesh sieve. Blend items 2 and 3 in a V-blender for 10 minutes. Coat items 2 and 3 using Aquacoat (FMC) aqueous polymer dispersion in a fluid bed column using a 10% by weight formula. Blend 50% of item 1 with items 4 and 5

for 10 minutes in a V-blender. Add remaining item 1, and blend again for 10 minutes. Blend item 7 with the mixture from the previous step for 10 minutes. Add item 6, and blend for 7 minutes. Compress 625 mg to the desired hardness using appropriate tooling.

Acetylsalicylic Acid Tablets (Direct Compression)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Acetylsalicylic acid (crystalline) (Merck)	400.00
99.00	2	Ludipress®	99.00
1.00	3	Stearic acid	1.00
15.00	4	Kollidon® CL	15.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with low compression force (hardness 90 N); 12-mm biplanar tablet has an average weight of 516 mg.

Acetylsalicylic Acid Tablets (Direct Compression)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Acetylsalicylic acid, 40 mesh	400.00
55.60	2	Cellulose (microcrystalline) (Avicel™ PH101)	55.60
21.40	3	Starch (pregelatinized)	21.40
2.20	4	Stearic acid	2.20
10.00	5	Croscarmellose sodium (Ac-Disol)	10.00
3.20	6	Fumed silica	3.20

MANUFACTURING DIRECTIONS

Screen about half of item 1 through a mill using 12-mesh screen with knives forward. Preblend items 2 to 6 with 25% of item 1, and pass the mixture through the mill. Pass

the balance of item 1 through the mill. Mix all the ingredients in a V-blender for 10 minutes, and compress using 13/32-inch tooling. For enteric coating, coat with Aquateric (FMC) dispersion.

Acetylsalicylic Acid Tablets (Direct Compression)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	2	Avicel™ PH101	200.00
15.00	3	Kollidon® 30	15.00
25.00	4	Kollidon® CL	25.00
3.00	5	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with low compression force of (hardness 61 N); 12-mm biplanar tablet has an average weight of 707 mg.

Acne Cover Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
37.00	1	Glyceryl stearate S/E	37.00
46.00	2	Mineral oil/lanolin alcohol (liquid base CB3939)	46.00
9.00	3	Polawax GP2000	9.00
18.00	4	Stearic acid	18.00
QS	5	Deionized water	QS
36.00	6	Propylene glycol	36.00
2.00	7	Carboxymethyl cellulose (CMC-7HF)	2.00
9.00	8	Magnesium aluminum silicate (regular) Veegum	9.00
9.00	9	Triethanolamine (99%)	9.00
120.00	10	Titanium dioxide	120.00
QS	11	Iron oxides	QS
50.00	12	Actives	50.00
QS	13	Perfume, preservative	QS

MANUFACTURING DIRECTIONS

Disperse CMC in propylene glycol and triethanolamine, and add warm water (60 to 65°C) while stirring, until the gum is hydrated. Add Veegum, and stir until hydrated. Heat oil phase to 60 to 65°C. Add water phase to oil phase

while stirring. Add pigments and stir to cool, adding the actives at 30°C. Homogenize using suitable equipment. Fill. Note that active ingredients may be added as required to this base formula.

Acne Scrub

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
20.00	1	Magnesium aluminum silicate magnabrite HV	20.00
582.00	2	Water	582.00
100.00	3	Propylene glycol	100.00
150.00	4	Mineral oil and acetylated lanolin alcohol	150.00
30.00	5	Glyceryl stearate and PEG-100 stearate	30.00
14.00	6	Myristyl propionate	14.00
100.00	7	PEG-600	100.00
4.00	8	Eucalyptus oil	4.00
QS	9	Preservatives	QS

MANUFACTURING DIRECTIONS

Slowly sift item 1 into water, mixing until smooth. Heat to 75°C. Heat items 3 to 6 separately; mix and heat to 70°C. Add this portion to item 1 dispersion, and mix well

until smooth. Add item 7 to mixture, and mix. Finally, add items 8 and 9, and mix until cool. If using parabens, prepare a solution in a portion of water and add before adding item 8 and after allowing parabens to cool to 50°C.

Acne Treatment Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
20.00	1	Polychol 10 (Laneth-10)	20.00
5.00	2	Lanolin alcohols (Super Hartolan)	5.00
55.00	3	Cetyl alcohol C90	55.00
60.00	4	Polawax, NF	60.00
14.00	5	Sulfur	14.00
QS	6	Deionized water	QS
40.00	7	Veegum® (regular)	40.00
20.00	8	Propylene glycol	20.00
20.00	9	Resorcinol	20.00
QS	10	Perfume, preservative	QS

MANUFACTURING DIRECTIONS

Hydrate Veegum in water. Add rest of the water-phase ingredients, and heat to 70°C. Heat oil phase to 70°C.

Disperse sulfur in the oil phase. Add oil phase to water phase while stirring. Stir to cool. Fill.

Aloe Vera Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
4.00	1	Aloe vera extract (200-fold)	4.00
50.00	2	Propylene glycol	50.00
QS	3	Preservative	QS
736.00	4	Water	736.00
11.00	5	Cremophor RH 40	11.00
QS	6	Perfume	QS
200.00	7	Lutrol F 127	200.00

MANUFACTURING DIRECTIONS

Prepare solutions I (items 1 to 4) and II (items 5 and 6) separately, and add I into II. Cool this mixture to <10°C

(or heat to 70 to 80°C), and dissolve item 7. Maintain the temperature until air bubbles escape. Appearance is clear, viscosity is about 60 Pa, and pH is about 5.5.

alpha-Bisabolol Aqueous Mouthwash Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
2.00	1	α -Bisabolol, natural (BASF)	2.00
QS	2	Flavor	QS
25.00	3	Cremophor RH 40	25.00
50.00	4	Glycerol	50.00
1.00	5	Saccharin sodium	1.00
QS	6	Preservative	QS
922.00	7	Water	922.00

MANUFACTURING DIRECTIONS

Heat mixture of items 1 to 3 to about 60°C, and slowly add the warm solution of items 4 to 7 (60°C). The clear, colorless liquid has a low viscosity.

alpha-Bisabolol Buccal or Topical Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
1.20	1	α -Bisabolol (racemic) (BASF)	1.20
10.00	2	Cremophor RH 40	10.00
0.10	3	Butylhydroxytoluene (BHT)	0.10
QS	4	Preservative	QS
990.00	5	Water	990.00

MANUFACTURING DIRECTIONS

Heat mixture of items 1 to 3 to about 60°C, stir well, and slowly add the warm solution of items 4 in 5 to obtain a clear solution.

alpha-Bisabolol Ethanolic Mouthwash Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
10.00	1	α -Bisabolol, racemic (BASF)	10.00
100.00	2	Flavor	100.00
60.00	3	Cremophor RH 40	60.00
10.00	4	Glycerol	10.00
2.00	5	Saccharin sodium	2.00
818.00	6	Ethanol (96%)	818.00

MANUFACTURING DIRECTIONS

Heat mixture of items 1 to 3 to about 60°C, and slowly add the warm solution of items 4 to 6. The clear, colorless liquid can be diluted with water.

alpha-Bisabolol Mouthwash Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
5.00	1	(-)- α -Bisabolol, natural (BASF)	5.00
50.00	2	Lutrol F 127	50.00
QS	3	Flavor	QS
100.00	4	Propylene glycol (Pharma)	100.00
300.00	5	Ethanol (96%)	300.00
545.00	6	Water	545.00

MANUFACTURING DIRECTIONS

Prepare solution of items 1 to 5, and slowly add the water.
The clear, colorless solution has pH 8.

Aluminum Hydroxide and Magnesium Carbonate Dry Syrup

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
200.00	1	Aluminum hydroxide dry gel (Giulini)	200.00
200.00	2	Basic magnesium carbonate	200.00
240.00	3	Kollidon® CL-M	240.00
211.50	4	Sorbitol (crystalline)	211.50
41.30	5	Orange flavor	41.30
82.60	6	Kollidon® 30	82.60
3.30	7	Coconut flavor	3.30
4.13	8	Banana flavor	4.13
4.13	9	Saccharin sodium	4.13
8.26	10	Water	8.26

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 5 with solution of items 6 to 10, pass through a sieve, and dry. Shake 58 g of the

granules with 100 mL of water. Product remains homogeneous and without sedimentation for more than 24 hours.

Aluminum Acetylsalicylate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Aluminum acetylsalicylate, excess	255.00
213.00	2	Mannitol	213.00
28.00	3	Corn starch	28.00
10.00	4	Kollidon® 90F	10.00
5.00	5	Lutrol E 6000	5.00
—	6	Isopropanol, QS	50.00 mL
23.00	7	Kollidon® CL	23.00
5.00	8	Magnesium stearate	5.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 3 with solution of items 7 and 8, and compress with medium compression force; 4 to 6, dry, pass through an 0.8-mm sieve, mix with items 12-mm biplanar tablet has an average weight of 540 mg.

Aluminum Hydroxide and Magnesium Hydroxide Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Aluminum hydroxide (Rorer)	200.00
200.00	2	Magnesium hydroxide (Rorer)	200.00
100.00	3	Lactose monohydrate	100.00
30.00	4	Kollidon® VA 64	30.00
QS	5	Water	260.00 mL
315.00	6	Sucrose (crystalline)	315.00
100.00	7	Sorbitol (crystalline) (Merck)	100.00
60.00	8	PEG-6000 (powder)	60.00
12.00	9	Aerosil® 200	12.00
6.00	10	Talc	6.00
6.00	11	Magnesium stearate	6.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 5 with solution of items 11, and press with high compression force (20 kN). The 4 to 5, dry, pass through an 0.8-mm sieve, add items 6 to 16-mm biplanar tablet has an average weight of 1013 mg.

Aluminum Hydroxide and Magnesium Hydroxide Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
320.00	1	Aluminum hydroxide (Dried Gel)	320.00
320.00	2	Magnesium hydroxide powder	320.00
32.00	3	Sucrose	32.00
288.40	4	Mannitol	288.40
QS	5	Povidone (Plasdone®) (10% solution in equal parts water and alcohol)	QS
12.90	6	Glycerin	12.90
19.20	7	Magnesium stearate	19.20
6.40	8	Fumed silica	6.40
0.30	9	Oil of peppermint	0.30

MANUFACTURING DIRECTIONS

Mix items 1 to 4 in a suitable blender; add item 6 to item 5, and use this combination to moisten the mix of items

1 to 4. Granulate by passing through a 20-mesh screen. Add and thoroughly mix items 7 to 9, and compress using 0.5-inch, flat-face, beveled-edge punches.

Aluminum Hydroxide and Magnesium Hydroxide Antacid Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
5.00	1	Purified bentonite (Veegum® HS)	5.00
2.00	2	Xanthan gum (Rhodigel)	2.00
401.00	3	Water	401.00
200.00	4	Sorbitol (70%)	200.00
360.00	5	Aluminum hydroxide gel	360.00
320.00	6	Magnesium hydroxide, USP	320.00
QS	7	Preservative, flavor	QS

MANUFACTURING DIRECTIONS

Slowly add a dry blend of item 1 and 2 to item 3, agitating with maximum available shear until a smooth and uniform

mix is obtained. Mix items 4 to 6 together in another vessel until uniform, and then add to previous mix. Agitate until uniform. Add item 7, and mix until uniform.

Aluminum Hydroxide and Magnesium Hydroxide Antacid Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
200.00	1	Magnesium aluminum silicate (Magnabrite S) (5% suspension)	200.00
2.00	2	Methyl paraben	2.00
1.00	3	Propyl paraben	1.00
0.50	4	Saccharin sodium	0.50
500.00	5	Aluminum hydroxide/magnesium hydroxide fluid gel	500.00
3.00	6	Polysorbate 80	3.00
2.00	7	Flavor	2.00
291.50	8	Deionized water	291.50

MANUFACTURING DIRECTIONS

Add the parabens and saccharin to item 1 with stirring until dissolved (may heat to 80°C to dissolve). Add item 5 with mixing. Finally, add item 6 and 7. Mix well.

Aluminum Hydroxide and Magnesium Hydroxide Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Quantity/L (g)
405.00	1	Aluminum hydroxide gel	290.00
100.00	2	Magnesium hydroxide paste (30%)	67.00
0.21	3	Ammonia solution (25%)	0.04
0.05	4	Ammonia solution (25%)	0.01
10.00	5	Methyl paraben	2.00
0.25	6	Menthol	0.05
3.00	7	Propyl paraben	0.60
1.00	8	Peppermint oil	0.20
50.00	9	Propylene glycol	10.00
1.25	10	Saccharin sodium	0.25
150.00	11	Sorbitol (70% solution)	30.00
4.50	12	Sodium hypochlorite (5%)	0.90
1.25	13	Sodium hypochlorite (5%)	0.25
15.00	14	Magnesium aluminum silicate (Veegum® HV)	3.00
QS	15	Purified water	QS to 1 L

Note: The quantity of the sodium hypochlorite solution should be adjusted according to the assay.

MANUFACTURING DIRECTIONS

Disperse item 14 in 60.0 g of hot purified water (70–80°C) in stainless steel vessel, using stirrer. Continue stirring for 30 minutes. Transfer the dispersion into mixer (e.g., Krieger) vessel by vacuum, and mix for 30 minutes at 16/32 mixer speed. Cool down to 30°C. Add 200.0 g of hot purified water (70 to 80°C) to the mixer. Mix and homogenize at 1420 rpm, mixer speed of 16/32, and vacuum of 0.5 bar for 30 minutes. Cool down to 30°C. Add 1.0 kg of purified water (70°C) to a suitable vessel, and heat to 85 to 90°C for 1 hour. Cool to 20 to 25°C. Mix items 13 and 4 and immediately add to purified water (20 to 25°C) in the storage vessel. Mix for 2 minutes. Store in a previously cleaned storage vessel. Load item 2 and 100.0 g of purified water (25 to 30°C) in a stainless steel mixing vessel with lid and stirrer. Mix for 5 minutes at medium speed. Transfer by vacuum into mixer. Load 80.0 g of item 1 and 80.0 g of purified water (25 to 30°C) from step above in a stainless steel mixing vessel with lid

and stirrer. Mix for 5 minutes at medium speed. Transfer by vacuum into mixer. Load 50.0 g of item 1 and 50.0 g of purified water (25 to 30°C) from step above in a stainless steel mixing vessel with lid and stirrer. Mix for 5 minutes at medium speed. Transfer by vacuum into mixer. Transfer item 11 into mixer by vacuum. Dissolve item 10 in 2.0 g of purified water (25 to 30°C), and transfer to mixer. Mix and homogenize for 30 minutes at 1420 rpm under vacuum of 0.5 bar. Dissolve items 5 and 7 in item 9 (50 to 60°C) by stirring in stainless steel container in a water bath. Dissolve items 8 and 6 and add to parabens/glycol solution. Mix well; add to mixer. Mix and homogenize for 10 minutes under vacuum of 0.5 bars. Mix items 12 and 3 and 2.0 g of purified water, and immediately add to the mixer. Mix for 10 minutes without vacuum. Add cold purified water to bring the volume up to 1 L. Mix for 15 minutes. Transfer the suspension through 630-µm sieve to the stainless steel storage tank. Final pH is 7.5 to 8.0, and density is 1.04 to 1.06.

Aluminum Hydroxide and Magnesium Hydroxide Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Quantity/L (g)
200.00	1	Aluminum hydroxide gel	214.00
80.00	2	Magnesium hydroxide paste (30%)	54.20
150.00	3	Sorbitol (70% solution)	30.00
10.00	4	Methyl paraben	2.00
1.00	5	Propyl paraben	0.20
2.00	6	Saccharin sodium	0.40
15.00	7	Magnesium aluminum silicate (Veegum® HV)	3.00
0.20	8	Ammonia solution (25%)	0.04
4.50	9	Sodium hypochlorite (5%)	0.90
100.00	10	Propylene glycol	20.00
0.75	11	Lemon mint flavor	0.15
QS	12	Purified water	QS to 1 L

MANUFACTURING DIRECTIONS

See previous entry for manufacturing directions.

Aluminum Hydroxide and Magnesium Hydroxide Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
40.00	1	Aluminum hydroxide	40.00
40.00	2	Magnesium hydroxide	40.00
50.00 g	3	Cremophor RH 40	50.00
1.00	4	Silicon oil DC 200 (Serva)	1.00
100.00	5	Kollidon® CL-M	100.00
QS	6	Water	76.90

MANUFACTURING DIRECTIONS

Mix Cremophor RH 40 well with the silicon oil, add the water, and suspend the solid substances.

Aluminum Hydroxide and Magnesium Hydroxide Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
405.00	1	Aluminum hydroxide gel (dried)	405.00
100.00	2	Magnesium hydroxide powder	100.00
108.00	3	Mannitol	108.00
38.80	4	Sorbitol powder	38.80
2.50	5	Saccharin sodium	2.50
16.70	6	Povidone (PVP K-30)	16.70
7.00	7	Magnesium stearate	7.00
2.00	8	Mint flavor (dry)	2.00
299.00	9	Purified water	299.00

MANUFACTURING DIRECTIONS

Dissolve items 4 and 5 in 59.0 g of purified water by using stirrer. Add item 6 while mixing until clear solution is obtained. Add items 1, 2, and 3 into mixer, and mix for 5 minutes using mixer and chopper at high speed. Dilute concentrate binding solution with 240.0 g of purified water. Add binding solution at a rate of 9 to 11 g/minute to the dry powders in mixer while mixing at low speed. Mix for 2 to 3 min. Scrape the sides, blade, and lid of the mixer. Mix and chop at low speed for an additional 2 to 3 minutes or until the granules stop flying around the chopper. Add extra purified water, if required, and continue mixing until a satisfactory mass is obtained. Record extra quantity of purified water added. Unload the wet mass into a clean Aeromatic bowl for drying. Avoid big lump formation, as this leads to nonuniform drying. Dry

the wet mass in an Aeromatic fluid-bed dryer at 60°C for 120 minutes. After 30 minutes of drying, scrape the semi-dried granules to break the lumps for uniform drying. Check the LOD (limit: NMT 5.5%). Pass the dried granules through 1.5-mm sieve using granulator at medium speed. Collect in stainless steel drums. Set aside 7 to 9 g granules for later step. Load the rest of the granules into blender. Pass items 8 and 7 through a sifter using a 250- μ m sieve. Collect in a polyethylene bag. Add about 7 to 9 g of granules, and mix gently. Load into blender, and blend for 3 minutes. Check temperature and humidity of the room before beginning compression (humidity limit: NMT 60%; temperature, 25 \pm 1°C). Compress the granules using a rotary tableting machine. Compress 680-mg tablets using 12.7-mm, flat, beveled-edge punches.

Aluminum Hydroxide and Magnesium Silicate Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
120.00	1	Aluminum hydroxide dried gel (Giulini)	120.00
250.00	2	Magnesium trisilicate	250.00
232.00	3	Ludipress®	232.00
6.00	4	Aerosil® 200	6.00
6.00	5	Magnesium stearate	6.00
12.00	6	Cyclamate sodium	12.00
1.50	7	Menthol	1.50

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with a compression force of 20 kN. Due to the poor flowability of the powder, the tableting machine should

be equipped with a special technical device to provide a continuous and homogeneous filling of the dies. The 16-mm biplanar tablet has an average weight of 640 mg.

Aluminum Hydroxide, Magnesium Carbonate (or Oxide), and Simethicone Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
576.00	1	Sucrose	576.00
157.00	2	Aluminum hydroxide	157.00
160.00	3	Magnesium carbonate (or oxide)	160.00
97.00	4	Magnesium oxide	97.00
45.00	5	Kollidon® 90 F	45.00
22.00	6	Aerosil® 200	22.00
300.00	7	Simethicone suspension (30%)	300.00
9.00	8	Menthol	9.00
1.00	9	Saccharin sodium	1.00
49.00	10	Talc	49.00
13.00	11	Magnesium stearate	13.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 6 with the simethicone suspension, dry, sieve through an 0.8-mm screen, add items 8 to 11, and press with high compression force. Tablet has an average weight of 1295 mg.

Aluminum Hydroxide, Magnesium Hydroxide, and Simethicone Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
27.00	1	Simethicone 30%	27.00
30.00	2	Cremophor RH 40	30.00
70.00	3	Water	70.00
80.00	4	Aluminum hydroxide dry gel (Giulini)	80.00
80.00	5	Magnesium hydroxide	80.00
90.00	6	Kollidon® CL-M	90.00
100.00	7	Sorbitol (crystalline)	100.00
4.00	8	Banana flavor	4.00
5.00	9	Coconut flavor	5.00
1.00	10	Saccharin sodium	1.00
QS	11	Water	QS to 1 L
QS	12	Citric acid (to adjust pH)	QS

MANUFACTURING DIRECTIONS

Mix Cremophor RH 40 with simethicone, and heat to about 50°C, stirring well. Add warm water. Dissolve the flavors and saccharin in water, and suspend aluminum

hydroxide, magnesium hydroxide, and Kollidon CL-M. Add emulsion of items 1 to 3 to the stirred suspension of items 4 to 11, and adjust the pH to about 9 with item 12, if needed.

Aluminum Hydroxide, Magnesium Hydroxide, and Simethicone Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Quantity/L (g)
215.00	1	Aluminum hydroxide gel	217.00
80.00	2	Magnesium hydroxide paste (30%)	56.00
25.00	3	Simethicone emulsion (Simethicone Antifoam M30)	18.50
150.00	4	Sorbitol (70% solution)	30.00
0.20	5	Ammonia solution 25%	0.04
10.00	6	Methyl paraben	2.00
1.00	7	Propyl paraben	0.20
28.00	8	Methylcellulose 4000 (Methocel A4M)	5.60
2.00	9	Saccharin sodium	0.40
4.50	10	Sodium hypochlorite (5%)	0.90
1.00	11	Lemon mint flavor	0.20
QS	12	Purified water	QS to 1 L

MANUFACTURING DIRECTIONS

See manufacturing directions for aluminum and magnesium hydroxide suspension.

Aluminum Hydroxide, Magnesium Hydroxide, and Simethicone Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1,000 Tablets (g)
200.00	1	Aluminum hydroxide gel (dried)	260.00
200.00	2	Magnesium hydroxide powder	200.00
200.00	3	Mannitol	200.00
45.00	4	Sorbitol powder	45.00
65.00	5	Dextrose (glucose) monohydrate	65.00
16.50	6	Povidone (PVP K-30)	16.50
2.50	7	Saccharin sodium	2.50
1.00	8	FD&C Yellow Dye No.10 lake	1.00
2.50	9	Mint flavor (dry)	2.50
1.50	10	Lemon flavor (dry)	1.50
25.00	11	Simethicone GS granules	84.00
315.00	12	Dextrates (Emdex®)	315.00
1.00	13	Colloidal silicon dioxide (Aerosil® 200)	1.00
6.00	14	Magnesium stearate	6.00
—	15	Purified water	160.00

MANUFACTURING DIRECTIONS

Processing should be done at relative humidity of $50 \pm 5\%$ and temperature of $26 \pm 1^\circ\text{C}$. Dissolve items 4, 5, and 7 in cold purified water (25 to 30°C) by using stirrer, then add item 6 while mixing. Add item 8, and disperse the color completely. Check final weight; if required, adjust with purified water. Load items 1, 2, and 3 into mixer and mix for 5 minutes using mixer and chopper at high speed. Add binding solution at a rate of 16 to 20 g/minute to the dry powders in mixer while mixing at low speed. Mix for 2 to 3 minutes. Scrape the sides, blade, and lid of the mixer. Mix and chop at low speed for an additional 2 to 3 minutes or until the granules stop flying around the chopper. Add extra purified water if required, and continue mixing until a satisfactory mass is obtained. Record extra quantity of purified water added. Unload the wet mass into clean Aeromatic bowl for drying. Avoid big lump

formation, as this leads to nonuniform drying. Dry the wet mass in an Aeromatic fluid-bed dryer at 60°C for 90 minutes. After 30 minutes of drying, scrape the semidried granules to break up the lumps to promote uniform drying. Pass the dried granules through a 1.5-mm sieve using a granulator at medium speed. Collect in stainless steel drums. Load the granules into blender. Add items 11 and 12 to stainless steel drum, and mix for 2 minutes using drum mixer, then load into the blender and mix along with the granules for 2 minutes. Pass items 9, 10, 13, and 14 through sifter using 250- μm sieve. Load the sieved material into blender and mix for 2 minutes. Unload into stainless steel drums. Check temperature and humidity of the room before beginning compression. Compress 1.2 g per tablet using 15.8-mm flat punch at relative humidity of $50 \pm 5\%$ at a temperature of $26 \pm 1^\circ\text{C}$.

Analgesic Clear Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
25.00	1	Hydroxypropyl cellulose	25.00
QS	2	Deionized water	QS to 1 kg
400.00	3	Ethanol DEB 100	400.00
100.00	4	Menthol	100.00
150.00	5	Methyl salicylate	150.00
25.00	6	DEA-oleath-3-phosphate	25.00

MANUFACTURING DIRECTIONS

Hydrate hydroxypropyl cellulose in water at 60 to 65°C. Stir to cool. Add ethanol. Add remaining ingredients, and stir until homogeneous.

Analgesic Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
130.00	1	Methyl salicylate	130.00
60.00	2	Menthol	60.00
20.00	3	Eucalyptus oil	20.00
5.00	4	Lanolin	5.00
1.00	5	Chloroxlenol	1.00
150.00	6	Glyceryl stearate and PEG-100 stearate	150.00
73.00	7	Cetearyl alcohol	73.00
70.00	8	Glyceryl stearate	70.00
QS	9	Deionized water	QS to 1 kg
QS	10	Preservative, color	QS

MANUFACTURING DIRECTIONS

Heat oil and water phases separately to 70°C. Add water phase to oil phase while stirring; stir to cool. Fill at 30°C.

Analgesic Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
150.00	1	Methyl salicylate	150.00
70.00	2	Menthol	70.00
10.00	3	Lanolin oil	10.00
30.00	4	PEG-40 stearate	30.00
20.00	5	Glyceryl stearate	20.00
QS	6	Deionized water	QS
1.50	7	Carbopol® 980	1.50
10.00	8	Potassium hydroxide (10% aqueous solution)	10.00
QS	9	Preservative, color	QS

MANUFACTURING DIRECTIONS

Heat oil and water phases (except potassium hydroxide) separately to 65 to 70°C. Add water phase to oil phase

while stirring. Add potassium hydroxide solution to neutralize. Stir to cool. Fill at 30°C.

Anise Oil Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
10.00	1	Anise oil	10.00
17.00	2	Cremophor RH 40	17.00
340.00	3	Ethanol	340.00
QS	4	Preservatives	QS
633.00	5	Water	633.00

MANUFACTURING DIRECTIONS

Mix the anise oil with Cremophor RH 40, heat to about 65°C, stir strongly, and slowly add the hot solution of

items 3 to 5 to produce a clear or slightly opalescent, colorless liquid.

Antazoline and Xylometazoline Eye Drops

Bill of Materials			
Scale (mg/100 mL)	Item	Material Name	Quantity/L (g)
500.00 g	1	Antazoline sulfate	5.00
50.00 g	2	Xylometazoline hydrochloride	0.50
0.15	3	Hydroxypropyl methylcellulose (4000 cps)	1.50
0.10	4	Benzalkonium chloride; use benzalkonium chloride solution (17%) (7% excess)	0.63 mL
0.10	5	Edetate disodium	1.00
0.843	6	Sodium chloride	8.43
QS	7	Water purified	QS to 1 L

MANUFACTURING DIRECTIONS

Equipment used should be thoroughly cleaned and rinsed before proceeding. Use steam-jacketed, glass-lined, or stainless steel (#304 or better) tank. The tank must be equipped with an agitator (preferably with speed control) and a cover to protect against air at all times during the manufacturing process, except when ingredients are being added or samples are being taken. Benzalkonium chloride markedly lowers the surface tension. During severe agitation or turbulent flow, substantial foaming will occur. This condition often exists in the processing equipment and in the overflow system of vacuum-filling machines. Benzalkonium chloride tends to concentrate in the foam. If the foam is not dissipated quickly and if it is allowed to accumulate, a substantial excess of benzalkonium chloride may result near the surface of the liquid after the foam condenses; therefore, it is advisable to design the processing and filling systems in such a way as to minimize

foaming and ensure rapid dissipation of any unavoidable foaming. Charge mixing tank to 90% of final volume with purified water. Heat water to 90°C and, while agitating, add and dissolve the hydroxypropyl methylcellulose by slowly sprinkling onto the surface of the water. Methylcellulose must be dispersed evenly over a period of time to ensure complete wetting and dispersion. The agitation rate should be adjusted to avoid excessive foaming. Allow 15 minutes for hydration of the hydroxypropylmethylcellulose before cooling. Discontinue heating and cool solution to ~40°C. While agitating, add and dissolve antazoline sulfate, xylometazoline hydrochloride, benzalkonium chloride, edetate disodium, and sodium chloride. Continue cooling to 25°C. Turn off agitator, and QS to final volume. Mix well. *Note:* Methylcellulose solutions filter at a slow rate; recirculate the solution through filter assembly until clear. Sterile-filter and fill.

Anti-Acne Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
422.00	1	Witch hazel (distilled, 14% alcohol)	422.00
5.00	2	Salicylic acid	5.00
5.00	3	Aloe vera gel	5.00
10.00	4	Sorbitol	10.00
500.00	5	Polyglycerylmethylacrylate	500.00
10.00	6	Propylene glycol	10.00
0.80	7	Methyl paraben	0.80
0.20	8	Propyl paraben	0.20

MANUFACTURING DIRECTIONS

Premix items 1 to 4. Add item 5 with low-shear mixing until homogeneous. Mix together items 6 to 8, and add them to the formulation.

Antifungal Foot Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
5.00	1	Dichlorbenzyl alcohol (Myacide SF)	5.00
5.00	2	Allantoin	5.00
200.00	3	Corn starch	200.00
790.00	4	Talc	790.00

MANUFACTURING DIRECTIONS

Mix all ingredients using geometric dilution technique.

Antiseptic Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
50.00	1	Polawax GP200	50.00
10.00	2	Lanolin	10.00
150.00	3	Mineral oil (70 cS)	150.00
70.00	4	Cetearyl alcohol	70.00
30.00	5	Dimethicone	30.00
QS	6	Deionized water	QS to 1 kg
5.00	7	Cetrimonium bromide	5.00
0.50	8	Chlorhexidine gluconate	0.50
QS	9	Perfume, preservative, color	QS

MANUFACTURING DIRECTIONS

Heat oil and water phases to 65°C. Add water phase to oil phase while stirring. Stir to cool. Fill.

Antiseptic Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
30.00	1	Cetearyl alcohol and cetareth-20	30.00
50.00	2	Mineral oil (70 cS)	50.00
2.00	3	Lanolin alcohol	2.00
QS	4	Deionized water	QS to 1 kg
5.00	5	Cetrimonium bromide (as 40% cetermide solution BP)	5.00
20.00	6	Glycerin	20.00
QS	7	Perfume, preservative, color	QS

MANUFACTURING DIRECTIONS

Heat oil and water phases separately to 70°C. Add water phase to oil phase while stirring. Stir to cool. Fill at 30°C.

Antiseptic Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
30.00	1	Cetearyl alcohol and ceteareth-20	30.00
45.00	2	Mineral oil (70 cS)	45.00
25.00	3	Stearyl alcohol	25.00
10.00	4	Lanolin	10.00
5.00	5	Polysorbate 60	5.00
15.00	6	Laneth-15	15.00
QS	7	Deionized water	QS to 1 kg
5.00	8	Cetrimonium bromide (as 40% ceterimide solution BP)	5.00
20.00	9	Glycerin	20.00
QS	10	Perfume, preservative, color	QS

MANUFACTURING DIRECTIONS

Heat oil and water phases separately to 70°C. Add water phase to oil phase while stirring. Stir to cool. Fill at 30°C.

Antiseptic Wet Wipes

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
3.75	1	Cetrimonium bromide	3.75
0.15	2	Chlorhexidine gluconate	0.15
10.0–20.0	3	Polysorbate 20	10.0–20.0
10.0–20.0	4	Glycerin	10.0–20.0
QS	5	Deionized water	QS to 1 L

MANUFACTURING DIRECTIONS

Preblend Polysorbate 20 and perfume. Combine remaining components with stirring; add perfume/Polysorbate 20 blend. Stir until clear. Package in wipes.

Aspartame Granules in Sachets

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Quantity/1000 Sachets (g)
30.00	1	Aspartame	30.00
2.00	2	Silicon dioxide (colloidal)	2.00
968.00	3	Cerelose powder N60 ^a	1052.00

^a Standard quantity of cerelose powder allows for LOD.

MANUFACTURING DIRECTIONS

Protect from moisture; maintain relative humidity of 40% and temperature of 25°C. Oven dry cerelose powder at 50°C overnight until LOD is NMT 3% (3 hours, vacuum at 60°C). Pass dried cerelose powder through 595-µm aperture screen in oscillating granulator. Charge the following ingredients into suitable blender: aspartame, half

of the amount of dried cerelose powder (milled), and colloidal silicon dioxide. Add the balance of the dried cerelose powder (for a total amount of dried powder of 968 g/kg), and blend for 15 minutes. Pass blended powders through an 840-µm screen using an oscillating granulator, and discharge into polyethylene-lined drums. Fill weight is 1 g/sachet.

Aspartame Powder in Sachets

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
47.50	1	Aspartame	47.50
2.50	2	Silicon dioxide (colloidal)	2.50
950.00	3	Mannitol granules	950.00

MANUFACTURING DIRECTIONS

Protect from humidity; maintain a relative humidity of 40% and a temperature of 25°C. Pass mannitol granules and colloidal silicon dioxide through an 840-µm screen in oscillating granulator. Charge the following ingredients into suitable blender: aspartame, half of the amount of

mannitol granules, and colloidal silicon dioxide. Add balance of mannitol granules, and blend for 15 minutes. Pass blended powders through an 840-µm screen using an oscillating granulator, and discharge into polyethylene-lined drums. Fill weight is 0.8 g/sachet.

Aspartame Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Aspartame	20.00
4.00	2	Cellulose (microcrystalline) (Avicel™ PH101), NF	4.00
4.00	3	Sodium starch glycolate (pH 5.5–7.5), NF International	4.00
0.50	4	Silicon dioxide (colloidal)	0.50
0.50	5	Povidone (PVP K-29–32), USP	0.50
14.00	6	Anhydrous alcohol (isopropyl, refined) USP	~14.00
34.00	7	Lactose (granulated)	34.00
4.00	8	Leucine, USP	4.00
3.00	9	Sodium benzoate (powder), NF	3.00

MANUFACTURING DIRECTIONS

Charge aspartame, cellulose microcrystalline, sodium starch glycolate, silicon dioxide, and Povidone in a suitable mixer. Blend for 20 minutes or until uniform. While mixing, slowly add isopropyl alcohol to blended powders until a suitable granulating mass is obtained. Avoid over-wetting. Pass wet mass through a 2.38-mm screen on an oscillating granulator and spread onto paper-lined trays. Oven dry at 45 to 50°C until LOD is NMT 1.2%. Pass

dried granulation through an 840-µm screen on an oscillating granulator. Charge dried granulation into a suitable mixer. Add granulated lactose, leucine, and sodium benzoate, and blend for ~10 minutes. Discharge into polyethylene-lined drums. Compress tablets in a low-humidity area not to exceed 40% relative humidity at 23°C. Compress, using 7/32-inch concave punches, to the following specifications: weight of 10 tablets is 0.7 g, thickness of a tablet is 2.9 to 3.3 mm.

Aspartame Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25	1	Aspartame	25
25	2	Dibasic calcium phosphate	25
3	3	Kollidon® VA 64	3
10	4	Water	10
3	5	Kollidon® CL	3
3	6	PEG-6000 (powder)	3

MANUFACTURING DIRECTIONS

Granulate mixture of items 1-3 with items 4 and 5, pass through an 0.8-mm sieve, mix with item 6, and press to tablets 60 mg in weight with a 5-mm biplanar shape.

Aspartame Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Aspartame	27.00
76.00	2	Ludipress®	76.00
12.00	3	Kollidon® CL	12.00
1.00	4	Magnesium stearate	1.00
3.00	5	Lutrol F 68	3.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press to tablets with low compression force. Each 8-mm biplanar tablet has an average weight of 120 mg.

Aspartame Tablets, Effervescent

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Aspartame	20.00
10.40	2	Sorbitol (crystalline)	10.40
14.30	3	Tartaric acid (powder)	14.30
18.70	4	Sodium bicarbonate	18.70
1.70	5	Kollidon® 25	1.70
1.10	6	PEG-6000 (powder)	1.10

MANUFACTURING DIRECTIONS

Mix, pass through a 0.5-mm sieve, and press to tablets. Each 6-mm biplanar tablet has an average weight of 66 mg.

Aspirin, Acetaminophen, and Caffeine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
225.00	1	Aspirin (40 mesh)	225.00
250.00	2	Acetaminophen (20 mesh)	250.00
30.00	3	Caffeine (granular)	30.00
100.00	4	Cellulose (microcrystalline) (Avicel™ PH-102)	100.00
45.00	5	Anhydrous lactose	45.00
10.00	6	Croscarmellose sodium (Ac-Di-Sol)	10.00
5.00	7	Fumed silica	5.00
10.00	8	Stearic acid	10.00

MANUFACTURING DIRECTIONS

Mix items 1 to 6 in a suitable blender. Pass the mixture through a mill using a 12-mesh screen with knives forward.

Add items 7 and 8, and blend the milled mixture for 20 minutes in a V-blender. Compress to tablet weight of 675 mg.

Aspirin, Acetaminophen, Caffeine, and Salicylamide Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Aspirin (40 mesh)	200.00
100.00	2	Salicylamide	100.00
100.00	3	Acetaminophen (40 mesh)	100.00
60.00	4	Caffeine (Granular)	60.00
150.00	5	Cellulose (microcrystalline) (Avicel™ PH101)	150.00
13.00	6	Stearic acid, USP	13.00
3.00	7	Fumed silica	3.00

MANUFACTURING DIRECTIONS

Screen all ingredients through a 20-mesh sieve. Blend all the ingredients in a V-blender for 20 minutes. Compress 615-mg tablets using 5/8-inch tooling.

Attapulgit Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
475.00	1	Attapulgit (regular)	475.00
275.00	2	Attapulgit (colloidal)	275.00
12.00	3	PVP K 30	12.00
7.00	4	Ac-Di-Sol	7.00
15.00	5	Kollidon® CL	15.00
30.00	6	Sucrose	30.00
50.00	7	Klucel® EF	50.00
40.00	8	Sucrose	40.00
35.00	9	Ac-Di-Sol	35.00
25.00	10	Kollidon® CL	25.00
14.00	11	Talc (fine powder)	14.00
5.00	12	Pectin	5.00
7.00	13	Glyceryl behenate	7.00
5.00	14	Aerosil 200	5.00
5.00	15	Magnesium stearate	5.00
—	16	Purified water	32.00
—	17	Ethanol (95%)	23.00

MANUFACTURING DIRECTIONS

Use face mask, hand gloves, and clean uniform. Avoid dust and inhalation of powder. Dissolve sucrose (item 6) in purified water by using an appropriate stirrer at slow speed in a stainless steel container. Dissolve Klucel EF in the ethanol by using an appropriate stirrer at slow speed in stainless steel container. Mix the two steps in a stainless steel drum by using an appropriate stirrer at slow speed. Take item 8 (sucrose) and pass through a Fitz mill using sieve number 24250 (impact forward, high speed). Collect in a stainless steel drum. Add items 1 to 5, and sift the material through a 500- μ m sieve using a Russell sifter. Mix for 3 minutes. Add the binding solution prepared earlier at a speed of 6 to 8 kg/minute to the dry powder in an appropriate mixer at slow speed. After addition, scrape sides and blades, then mix and chop further for 1 minute at slow speed. Check for satisfactory wet mass. Add additional purified water, if required, to obtain satisfactory wet mass. Spread the granules onto stainless steel trays to a thickness of 1/4th of the tray thickness, and load

the trays on the trolley. Load the trolleys into the oven, and dry the granules at 55°C for 16 hours. After 4 hours of drying, stir the granules on the trays and change the position of the trays for uniform drying. Check the LOD of dried granules (limit: 2.5 to 3.5%). The LOD should be strictly maintained; otherwise, tablet hardness and friability are affected. If required, dry further to obtain the desired LOD. Grind the dried granules first using a 2.5-mm sieve and then a 1.25-mm sieve. Load the ground material into a double-cone blender. Sift items 9, 10, 12, and 14 through a 500- μ m sieve, and add mixture to the double-cone blender. Mix for 5 minutes. Sift items 11, 13, and 15 through a 250- μ m sieve, and collect in a polyethylene bag. Add about 2 to 3 kg bulk granules from earlier step, mix, and add to the double-cone blender. Mix for 1 minute. Compress the granules using an 18 \times 8-mm, oblong, capsule-shaped, parallel, concave, plain punch for a 1-g tablet weight of hardness 12 to 18 kp. Coat the tablets using one of the HPMC coating solutions (see Appendix).

Baby Cream, Benzalkonium Chloride and Zinc Oxide

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
0.002 mL	1	Benzalkonium chloride solution	2.30 mL
85.00 mg	2	Zinc oxide (powder)	85.00
100.00 mg	3	Polawax (emulsifying, nonionic wax)	100.00
16.00 mg	4	Alcohol cetostearyl	16.00
4.00 mg	5	Lanolin (acetylated/anhydrous, regular)	4.00
80.00 mg	6	Glycerin (96%)	80.00
10.00 mg	7	Oil (neutral, vegetable triglycerides mixture; Miglyol®)	10.00
0.50 mg	8	Propyl paraben (Aseptoform™ P)	0.50
1.00 mg	9	Methyl paraben (Aseptoform™ M)	1.00
0.80 mL	10	Purified water	QS to 800.00 mL
0.24 mg	11	Perfume (Diabolo 110.388/B)	0.24

MANUFACTURING DIRECTIONS

Avoid mixing air into emulsion. Emulsify under vacuum to minimize air entrapment. Use jacketed tank with vacuum with high-speed agitator (adjustable, slow-speed, anchor type with Teflon sweep blades). If necessary, mill zinc oxide in a Fitz mill or similar device (impact forward, maximum speed), fitted with a 250- μ m screen. Repeat three times. Heat 800 mL of water to 75°C in a steam-jacketed mixing tank, and dissolve methyl paraben. Maintain temperature at 75°C. Disperse milled zinc oxide in solution of previous step. Maintain temperature at 75°C. Dissolve benzalkonium chloride and glycerin in solution, and maintain temperature at 75°C. In a separate steam-jacketed tank, add Polawax, cetostearyl alcohol, acety-

lated lanolin, oil, and propyl paraben; carefully melt at 70°C. Adjust the turbo-mixer of the steam-jacketed tank containing the aqueous phase to maximum speed, keeping the temperature at 75°C. Slowly add the oil phase to the aqueous phase. Generate as much vacuum as possible, and maintain it for the rest of the process. Circulate cold water to allow for a very slow temperature decrease (down to 60°C). Stop the turbo-mixer and set the anchor-type agitator at minimum speed until 40 to 45°C is reached. The temperature decrease must be very slow. Break the vacuum, and add perfume to cream with anchor-type agitator set at slow speed. Continue to mix until the perfume is completely dispersed.

Baby Lotion

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L
50.00	1	Alcohol (ethanol; natural cosmetic grade)	50.00 g
50.00	2	Propylene glycol	50.00 g
0.80	3	Ethoxylated nonyl phenol	0.80 g
0.005	4	FD&C Red Dye No. 40	5.70 mg
0.41	5	FD&C Blue Dye No. 1	0.41 g
0.70	6	FD&C Yellow Dye No. 5	0.70 g
0.40	7	Perfume essence (Nelandia)	0.40 g
QS	8	Hydrochloric acid (reagent-grade bottles)	~0.01 g
QS	9	Purified water	QS to 1.00 L

MANUFACTURING DIRECTIONS

Use 316 or more resistant-grade stainless steel tank. Charge approximately 800 ml of purified water in main mixing tank. Add alcohol and propylene glycol, and mix for 5 minutes. Separately dissolve each dye in sufficient water to obtain 0.5% dye solutions. Add color solutions to main tank, and mix. Rinse containers with small

portions of purified water, and add rinsings. Dissolve perfume essence in ethoxylated nonyl phenol. Add solution from previous step to main tank, and mix for 5 minutes. Determine pH of solution, and adjust if necessary with 5% hydrochloric acid solution. Mix well; pH should be 5.7 to 5.9. QS to 1 L with purified water.

Baby Shampoo

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg
250.00	1	Sodium alkyl ether sulfate/sulfonate	250.00 g
30.00	2	Monateric CAB surfactant	30.00 g
30.00	3	Cocamide DEA surfactant (Synotol CN 90)	30.00 g
1.00	4	Methylparaben	1.00 g
0.52	5	Anhydrous citric acid	0.52 g
0.003	6	FD&C Yellow Dye No. 6	3.50 mg
0.01	7	FD&C Yellow Dye No. 5	15.00 mg
4.00	8	Ethoxylated nonyl phenol	4.00 g
3.00	9	Perfume I	3.00 g
1.00	10	Perfume II	1.00 g
8.50	11	Sodium chloride	8.50 g
QS	12	Purified water	QS to 1.00 kg

MANUFACTURING DIRECTIONS

Use 315 or more resistant-grade stainless steel tank. Add approximately 270 g of purified water to the main mixing tank. With slow agitation add cocamide DEA surfactant. Add and dissolve methyl paraben, and mix for approximately 10 minutes. Add the following ingredients to tank: sodium alkyl sulfate/sodium alkyl ether sulfate/sulfonate, monateric CAB surfactant, and ~280 g of purified water. Mix for 15 minutes until complete solution is obtained. With constant stirring, slowly add citric acid (10% solution) until a pH of 6.9 to 7.1 is maintained constantly for

5 minutes after the last addition of the citric acid solution. Separately dissolve FD&C Yellow Dyes No. 6 and 5 (if used) in sufficient purified water. Add dye solution from step above to main tank, and mix. Rinse containers with a small portion of purified water, and add rinsings. Separately mix ethoxylated nonyl phenol with perfumes (perfume available from Firmenich; Plainsboro, NJ), and add to main mixing tank. Rinse container with purified water, and add rinsing. Mix until completely dissolved. Slowly add in small portions sodium chloride to adjust the viscosity to between 1500 and 3500 cps. Mix for 15 minutes. If necessary, QS to 1 kg with purified water.

Basic Cream for Various Active Ingredients

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
70.00	1	Cetylstearyl alcohol	70.00
15.00	2	Cremophor A 6	15.00
15.00	3	Cremophor A 25	15.00
120.00	4	Liquid paraffin	120.00
2.00	5	Parabene(s)	2.00
680.00	6	Water	680.00
80.00	7	Propylene glycol	80.00
1.00–20.00	8	Active ingredient	1.00–20.00

MANUFACTURING DIRECTIONS

Separately heat a mixture of items 1 to 5 and the water to about 80°C. Add the water to the obtained solution with rigorous stirring. Heat items 7 and 8 until the active

ingredient is dissolved, mix with aqueous solution, and continue to stir during cooling to room temperature. This white basic cream can be readily used for active ingredients soluble in 1,2-propylene glycol.

Benzalkonium Chloride Contraceptive Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
50.00	1	PEG-6, PEG-32, and glycol stearate (Tefose® 63)	50.00
30.00	2	Apricol kernel oil PEG-6 esters (Labrafil® M 1944 CS)	30.00
816.00	3	Deionized water	816.00
80.00	4	Hydroxyethylcellulose	80.00
24.00	5	Benzalkonium chloride (50 wt% in water)	24.00

MANUFACTURING DIRECTIONS

Mix items 3 and 4 at room temperature. Heat to 75°C, and add items 1 and 2 while stirring. Cool with gentle stirring to 30°C, then add item 5 and stir.

Benzoyl Peroxide and α -Bisabolol Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
2.00	1	α -Bisabolol, natural (BASF)	2.00
60.00	2	Propylene glycol	60.00
100.00	3	Triethanolamine	100.00
30.00	4	Cremophor RH 40	30.00
30.00	5	Kollidon® 30	30.00
408.00	6	Water	408.00
10/00	7	Carbopol® 940	10/00
400.00	8	Water	400.00
50.00	9	Benzoyl peroxide	50.00

MANUFACTURING DIRECTIONS

Prepare suspension of items 7 and 8; let swell for 1 hour.

Add this suspension to the well-stirred solution of items 1 to 5. Add item 9 to produce a colorless, transparent gel.

Benzoyl Peroxide Anti-Acne Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
460.50	1	Deionized water	460.50
5.00	2	Carbomer 940	5.00
10.00	3	Hydroxypropyl methylcellulose (HPMC; medium viscosity)	10.00
137.50	4	Deionized water	137.50
70.00	5	Purified bentonite (Polargel, NF)	70.00
2.00	6	Methyl paraben	2.00
1.00	7	Propyl paraben	1.00
20.00	8	Glyceryl stearate	20.00
60.00	9	Propylene glycol	60.00
20.00	10	PEG-600	20.00
20.00	11	Myristyl propionate	20.00
50.00	12	Dimethicone	50.00
70.00	13	Purified bentonite (Polargel®, NF)	70.00
10.00	14	Titanium dioxide	10.00
100.00	15	Benzoyl peroxide (70%)	100.00

MANUFACTURING DIRECTIONS

Sift Carbomer 940 into vortex in water; when completely dispersed, sift in the HPMC. Add parabens with stirring, and heat to at least 80°C until dissolved. Add glyceryl stearate. Blend in propylene glycol and items 10 to 13 in

order, and mix well. After addition of the Polargel, allow 15 minutes of mixing to complete hydration. Blend propylene glycol portion into the first part. Finally, add benzoyl peroxide and titanium dioxide to the mixture and mill.

Benzoyl Peroxide Anti-Acne Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
2.50	1	Acrylates/C10-30 alkyl acrylate cross-polymer (Permulen TR1)	2.50
4.00	2	Carbopol® 980	4.00
QS	3	Deionized water	QS to 1 kg
40.00	4	Isopropyl myristate	40.00
10.00	5	Cetyl alcohol	10.00
20.00	6	Glyceryl stearate	20.00
50.00	7	Sodium hydroxide (0.5-M)	50.00
15.00	8	Deionized water	15.00
50.00	9	Benzoyl peroxide	50.00
50.00	10	PEG-600	50.00
QS	11	Perfume, preservative	QS

MANUFACTURING DIRECTIONS

Hydrate Carbopol and Permulen in warm water at 60°C. When fully hydrated, heat to 70°C. Heat oil phase to 70°C. Add water phase to oil phase while stirring. Add sodium

hydroxide, and continue stirring. Combine benzoyl peroxide, PEG-600, and deionized water, and add to the emulsion. Homogenize at 35°C with caution, using suitable equipment.

Benzoyl Peroxide Anti-Acne Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
40.00	1	Purified bentonite (Polargel®, NF)	40.00
10.00	2	Hydroxypropyl methylcellulose (HPMC)	10.00
522.20	3	Water	522.20
190.00	4	Water	190.00
2.00	5	Methyl paraben	2.00
2.00	6	Propyl paraben	2.00
20.00	7	Glyceryl stearate	20.00
60.00	8	Propylene glycol	60.00
20.00	9	Myristyl propionate	20.00
5.00	10	Dimethicone	5.00
QS	11	Iron oxides	QS
10.00	12	Titanium dioxide	10.00
100.00	13	Benzoyl peroxide (77%)	100.00

MANUFACTURING DIRECTIONS

Sift the Polargel into water with rapid mixing. Allow to hydrate for 15 minutes. Pass HPMC through a coarse sieve, add to the Polargel solution, and mix until all lumps are removed. Add parabens to the water with stirring, and

heat to 90°C to dissolve the parabens. Add items 4 to 10 and mix well, then add these to the HPMC mixture. Mix well again. Finally add items 11 to 13, and mix. Mill product.

Benzoyl Peroxide Anti-Acne Microemulsion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
470.00	1	Ethoxydiglycol (Transcutol®)	470.00
250.00	2	PEG-8 caprylic/capric glycerides (Labrasol®)	250.00
150.00	3	Dipelargonate propylene glycol (DPPG)	150.00
80.00	4	Benzoyl peroxide	80.00
50.00	5	Propylene glycol laurate (Lauroglycol®)	50.00

MANUFACTURING DIRECTIONS

Mix items 1 to 3. Dissolve item 4 in this mixture with mixing for 1.5 to 2.0 hours; add item 5 to mixture, and mix until uniform emulsion is obtained.

Benzyl Benzoate Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
100.00	1	Benzyl benzoate	100.00
220.00	2	Cremophor RH 40	220.00
410.00	3	Ethanol (96%)	410.00
270.00	4	Water	270.00

MANUFACTURING DIRECTIONS

Heat the mixture of benzyl benzoate and Cremophor RH 40 to about 60°C. Stir strongly, and slowly add the water. Finally, add the ethanol to produce a clear, colorless liquid.

Berberine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Berberine sulfate	5.70
54.10	2	Lactose monohydrate	54.10
54.10	3	Ludipress®	54.10
1.20	4	Magnesium stearate	1.20

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with low compression force. The 6-mm biplanar tablet has an average weight of 115 mg.

Beta-Carotene Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
7.00 mg	1	Beta-carotene; use Lucarotin® CWD (dry powder, 10%) (BASF)	70.00
113.00 mg	2	Ludipress®	113.00
200.00 mg	3	Anhydrous citric acid	200.00
120.00 mg	4	Sodium bicarbonate	120.00
12.00 mg	5	Sodium carbonate	12.00
20.00 mg	6	Sodium cyclamate	20.00
15.00 mg	7	Aspartame	15.00
20.00 mg	8	Orange flavor	20.00
30.00 mg	9	PEG-6000 (powder)	30.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with medium or high compression force at maximum

30% relative humidity. Use 12-mm biplanar punches for 602-mg tablets.

Beta-Carotene Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
15.00	1	Beta-carotene (dry powder, 10% with excess)	160.00
240.00	2	Ludipress®	240.00
175.00	3	Dicalcium phosphate, granulated with 5% Kollidon® 30	175.00
6.00	4	Kollidon® CL	6.00
2.00	5	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with medium compression force. Compress 400 mg in 12-mm biplanar punches.

Beta-Carotene Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
15.00	1	Beta-carotene (dry powder, 10%)	150.00
175.00	3	Dicalcium phosphate, granulated with 5% Kollidon® 30	175.00
100.00	4	Avicel™ PH101	100.00
5.00	5	Kollidon® CL	5.00
2.50	6	Aerosil® 200	2.50
20.00	7	Talc	20.00
2.50	8	Calcium arachinate	2.50

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with a medium compression force. Compress 502 mg in 12-mm biplanar punches.

Beta-Carotene Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Beta-carotene (dry powder, 10%)	220.00
250.00	2	Avicel™ PH101	250.00
20.00	3	Kollidon® CL	20.00
2.00	4	Aerosil® 200	2.00

MANUFACTURING DIRECTIONS

Mix all components, and press with a low compression force. Compress 518 mg in 12-mm biplanar punches.

Beta-Carotene, Vitamin C, and Vitamin E Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Beta-carotene (dry powder, 10%)	100.00
250.00	2	Ascorbic acid (crystalline) (BASF)	250.00
280.00	3	Sodium ascorbate (crystalline)	280.00
500.00	4	Vitamin E acetate (dry powder, SD 50)	500.00
600.00	5	Sorbitol (crystalline)	600.00
500.00	6	Ludipress®	500.00
350.00	7	Fructose	350.00
50.00	8	PEG-6000 (powder)	50.00

MANUFACTURING DIRECTIONS

Mix all components, pass through a sieve, and press with high compression force. The 20-mm biplanar tablet has an average weight of 2.6 g.

Beta-Carotene, Vitamin C, and Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
12.00	1	Beta-carotene (dry powder, 10% with excess)	125.00
125.00	2	Ascorbic acid (crystalline) (BASF)	125.00
141.00	3	Sodium ascorbate (crystalline) (BASF)	141.00
250.00	4	Vitamin E acetate (dry powder, SD 50)	250.00
119.00	5	Ludipress® or sorbitol (crystalline)	119.00
5.00	6	PEG-6000 (powder)	5.00
15.00	7	Orange flavor (FDO)	15.00
10.00	8	Sodium cyclamate	10.00

MANUFACTURING DIRECTIONS

Mix all components, pass through a sieve, and press with medium compression force. Compress 790 mg into 12-mm biplanar tablets.

Beta-Carotene, Vitamin C, and Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
6.00	1	Beta-carotene; use Betavit® (dry powder, 10% with excess) (BASF)	65.00
100.00	2	Ascorbic acid (powder) (BASF)	100.00
60.00	3	Vitamin E acetate (dry powder, 50%)	60.00
369.00	4	Ludipress®	369.00
6.00	5	Magnesium stearate	6.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix and press with medium or high compression force. Compress 599 mg into 12-mm biplanar tablets.

Beta-Carotene, Vitamin C, and Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
6.00	1	Beta-carotene; use Betavit® (dry powder, 10% with excess) (BASF)	65.00
100.00	2	Ascorbic acid (powder) (BASF)	100.00
60.00	3	Vitamin E acetate (dry powder, 50%)	60.00
233.00	4	Sorbitol (crystalline) (Merck)	233.00
30.00	5	Kollidon® VA 64	30.00
8.00	6	Kollidon® CL	8.00
4.00	7	Magnesium stearate	4.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with medium or high compression force. Compress 502 mg into 12-mm biplanar tablets.

Beta-Carotene, Vitamin C, and Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
7.00	1	Beta-carotene; use Betavit® (dry powder, 10% with excess) (BASF)	75.00
60.00	2	Ascorbic acid (powder) (BASF)	60.00
50.00	3	Vitamin E acetate (dry powder, 50%)	50.00
240.00	4	Sorbitol (crystalline)	240.00
30.00	5	Kollidon® CL	30.00
5.00	6	Magnesium stearate	5.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with low compression force. A colorant pigment

should be added to obtain a homogeneous appearance of tablets. Use 12-mm biplanar punches for 497-mg tablets.

Betamethasone and Neomycin Gel-Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
1.30	1	Betamethasone valerate	0.13
6.50	2	Neomycin sulfate	0.65
150.00	3	Lutrol E 400	15.00
100.00	4	Miglyol® 812	10.00
200.00	5	Lutrol F 127	20.00
QS	6	Water	QS to 1 kg

MANUFACTURING DIRECTIONS

Dissolve betamethasone valerate in a mixture of Lutrol E 400 and Miglyol 812. Dissolve Lutrol F 127 and neomycin

sulfate in water at 5 to 10°C. Mix both solutions. Maintain cool temperature until the air bubbles disappear. A milky white, soft gel-cream is obtained.

Betamethasone Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
70.00	1	Cetylstearyl alcohol	70.00
15.00	2	Cremophor A 6	15.00
15.00	3	Cremophor A 25	15.00
12.00	4	Liquid paraffin	12.00
2.00	5	Parabene(s)	2.00
697.00	6	Water	697.00
80.00	7	Propylene glycol	80.00
1.00	8	Betamethasone	1.00

MANUFACTURING DIRECTIONS

Heat the mixture of items 1 to 5 and item 6 separately to about 80°C. Add together with rigorous stirring. Heat

items 7 and 8 until the active ingredient is dissolved. Mix with above mixture, and continue to stir to cool to room temperature to produce white cream.

Betamethasone Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
1.00	1	Betamethasone valerate	1.00
100.00	2	Ethanol (96%)	100.00
200.00	3	Propylene glycol	200.00
220.00	4	Lutrol F 127	220.00
QS	5	Water QS	470.00

MANUFACTURING DIRECTIONS

Prepare a solution of items 1 to 3 at room temperature and a solution of items 4 and 5 at about 6°C (or at >70°C). Mix both solutions. Maintain the temperature until the air

bubbles disappear. A certain amount of propylene glycol could be substituted by water. The obtained gel is clear and colorless.

Betamethasone Valerate Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Quantity/kg (g)
0.10	1	Betamethasone valerate (34% excess)	1.34
2.00	2	Poloxyl 20 cetostearyl ether (Cetomacrogol 1000)	20.00
8.00	3	Cetostearyl alcohol	80.00
0.10	4	Methyl paraben	1.00
0.034	5	Propyl paraben	0.34
0.10	6	Chlorocresol	1.00
6.00	7	Mineral oil (liquid paraffin)	60.00
0.29	8	Monobasic sodium phosphate	2.90
17.80	9	Petrolatum (soft white paraffin)	178.00
66.00	10	Purified water	660.00

MANUFACTURING DIRECTIONS

Heat item 10 to 90°C in mixer. Dissolve items 4 and 5 (parabens) to a clear solution by stirring. Dissolve 3.0 g of item 2 in the parabens solution while stirring. Dissolve items 6 and 8 in the parabens solution while stirring. Set the mixer at a temperature of 65 to 70°C and speed at 8 rpm; use manual mode. Load 17.0 g of item 2, item 9, item 3, and 45.0 g of item 7 in a fat melting vessel. Heat to 70 to 75°C while stirring. Maintain temperature at 65 to 75°C. Mix item 1 in 10.0 g of item 7 in a stainless steel container. Homogenize for 10 minutes to make a smooth slurry. Check the temperature of the aqueous phase in the mixer (should be 65 to 70°C). Check the temperature of the fatty phase in the fat melting vessel (should be 65 to 70°C). Set the mixer speed 8 rpm and vacuum at 0.4 to 0.6 bar. Transfer the fatty phase to the aqueous phase in

mixer vessel through filter under vacuum, while mixing. Start the homogenizer at high speed. Homogenize for 10 minutes. Check and record the pH of cream (limit 4.5 to 5.2 at 30°C). Cool the temperature to 50°C while mixing. Release the vacuum. Take out 400 g of the cream into the stainless steel vessel, and set aside. Add slurry from earlier step to the remaining cream base in mixer. Rinse the container of slurry using 5.0 g of item 7 and transfer the rinsing to the mixer. Homogenize for 10 minutes at high speed (mixer speed, 8 rpm). Load 400 g cream from step above to the mixer. Set the mixer in manual mode at 8 rpm and a vacuum of 0.4 to 0.6 bar. Homogenize at high speed with recirculation, temperature 25°C. Homogenize for 10 minutes with recirculation, stop the homogenizer, and continue mixing to produce a white, homogeneous cream of pH 4.5 to 5.2 at 30°C.

Betamethasone Valerate Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Quantity/kg (g)
0.10	1	Betamethasone; use betamethasone valerate	1.30
84.87	2	Petrolatum (soft white paraffin)	848.70
15.00	3	Mineral oil (liquid paraffin)	150.00

MANUFACTURING DIRECTIONS

Melt item 2 in a fat melting vessel at 75°C while mixing (do not overheat item 2). Maintain temperature of the molten mass in the melting vessel at 60 to 65°C. Start the steam on the mixer vessel, and set the temperature at 60°C. Transfer 160.0 g of the molten mass at 60°C to the mixer vessel. Retain the rest of the quantity in the fat melting vessel. Start mixing in the mixer vessel at medium speed with a vacuum between 0.4 and 0.6 bar until obtaining actual temperature of 40 to 45°C. Maintain the temperature of mixer vessel at 40 to 45°C. Add item 1 in 80.0 g of item 3, and homogenize for 3 minutes using a homog-

enizer. Keep the slurry aside. Rinse the homogenizer and container with 70.0 g of item 3. Transfer item 1 slurry from step above and the rinsing from previous step to the mixer vessel. Start mixing under a vacuum of 0.4 to 0.6 bar for 15 minutes. The temperature should be maintained at 40 to 45°C. Slowly transfer the rest of the quantity of molten mass (temperature, 60°C) into mixer vessel, continue mixing for 5 minutes after each addition. At the end of addition, mix an additional 10 minutes under a vacuum of 0.4 to 0.6 bar. Homogenize for 5 minutes at high speed under a vacuum of 0.4 to 0.6 bar. Cool the ointment to 30 to 35°C with stirring under a vacuum of 0.4 to 0.6 bar.

Bisacodyl Delayed-Release Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
05.00	1	Bisacodyl	5.00
20.00	2	Cellulose (microcrystalline) (Avicel™ PH102)	20.00
45.27	3	Lactose (spray dried) ^a	45.27
04.00	4	Maize starch (dried) ^b	4.00
00.73	5	Magnesium stearate	0.73

^a Particle size distribution: minimum, 98% 250 µm, 30 to 60% 100 µm; maximum 15% 45 µm.

^b LOD NMT 4.5%, when dried at 120°C for 4 hours.

MANUFACTURING DIRECTIONS

Handle bisacodyl carefully; it can cause itching if it comes into contact with skin. Over-mixing of lubricants reduces the hardness. Check the temperature and relative humidity of the room before beginning processing. Limit relative humidity to 50 to 60% and temperature to 27 to 30°C. Mix items 1 and 2 in a stainless steel drum for 2 to 3 minutes. Pass the mixed powder through a 500-µm sieve using sifter. Collect in stainless steel drum. Pass item 3 through a 500-µm sieve using sifter. Collect in stainless

steel drum. Load the sieved material into the drum mixer, and mix for 5 minutes. Mix items 4 and 5 in a polyethylene bag for 1 minute. Pass the mix through a 250-µm sieve. Collect in a polyethylene bag. Add 3 to 5 g powder to it, and mix for 1 minute. Add this mixture, and mix for 1 minute in a drum blender. Check the moisture content (limit: 1.0 to 1.5%). Compress the granules using a rotary tableting machine; 6-mm biconvex tablets have an average weight of 750 mg and hardness of 4 to 5 kp. Apply enteric coating.

Bisacodyl Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Quantity/1000 Suppositories (g)
5.00	1	Bisacodyl (micronized) (2% excess) ^a	5.10
447.50	2	Hard fat (Witepsol E 76)	447.50
447.50	3	Hard fat (Witepsol W 45)	447.50

^a 100% particles should be less than 70 µm; Fill weight is 1800 mg per suppository.

MANUFACTURING DIRECTIONS

The molten suppository mass must be kept stirred throughout the storage period and during manufacturing and filling to avoid sedimentation of the active drug. The active ingredient causes skin irritation which vanishes after some time without after-effects. Avoid dust formation during processing. In particular, protect eyes and mucous membranes. Load items 2 and 3 into the fat melting vessel, and heat to $50 \pm 3^\circ\text{C}$. Transfer the molten mass to a mixer through 0.8 mm sieve. Set the temperature at $40 \pm 2^\circ\text{C}$. Load item 1 to the mixer containing molten mass. Carefully mix the powder with the molten mass. Set the mixer

at a temperature of $40 \pm 2^\circ\text{C}$ and speed of 10 rpm (manual mode), and mix for 20 minutes. Set the mixer at a temperature of $40 \pm 2^\circ\text{C}$, speed of 10 rpm (manual mode), and vacuum of 0.6 bar. Homogenize at low speed while mixing for 10 minutes. Homogenize at high speed while mixing for 3 minutes. Continue mixing of the mass under vacuum in mixer. Heat the storage vessel, and set the temperature at $40 \pm 2^\circ\text{C}$. Transfer the molten mass from the mixer to the storage vessel. Hold the mass at $40 \pm 2^\circ\text{C}$, continuously mixing at low speed. Fill weight is 900 mg per suppository. Use a fill weight of 1.8 g for 10-mg suppositories.

Bismuth Carbonate Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
266.66 mg	1	Light kaolin	266.66
8.30 mg	2	Pectin	8.30
6.70 mg	3	Bismuth carbonate	6.70
9.40 mg	4	Cellulose (microcrystalline; Avicel™ RC-591)	9.40
1.40 mg	5	Methylparaben	1.40
0.20 mg	6	Saccharin sodium	0.20
0.40 mg	7	Aspartame	0.40
40.00 mL	8	Sorbitol	40.00 mL
5.00 mL	9	Ethanol	5.00 mL
QS	10	Deionized water	QS to 1 L

MANUFACTURING DIRECTIONS

Dissolve item 2 in hot water. Disperse item 1 in 75 mL of item 10 at room temperature. With constant agitation, add item 3 and continue stirring. Mix and cool to room temperature. Disperse item 4 in item 10, and add it to the

batch. Dissolve item 2 in item 1 dispersion, and add to the batch. Dissolve items 6 and 7 in water, and add to the batch. Add flavor, color, and water to volume. Pass through homogenizer or colloid mill if necessary.

Bismuth Subsalicylate Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
15.00	1	Magnesium aluminum silicate (Magnabrite K)	15.00
1.50	2	Methylcellulose	1.50
910.00	3	Deionized water	910.00
0.50	4	Saccharin sodium	0.50
30.00	5	Bismuth subsalicylate	30.00
4.00	6	Salicylic acid	4.00
10.00	7	Sodium salicylate	10.00
29.00	8	Ethanol	29.00
QS	9	Preservatives	QS
QS	10	Colorings	QS

MANUFACTURING DIRECTIONS

Dry blend items 1 and 2, and slowly add them to item 3, gradually mixing well each time. Finally add items 8 to 10 to smooth mix.

Bran Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Bran wheat (milled <1 mm)	250.00
200.00	2	Ludipress®	200.00
5.00	3	Kollidon® 30	5.00
4.00	4	Aerosil® 200	4.00
4.00	5	Magnesium stearate	4.00

MANUFACTURING DIRECTIONS

Mix all components, pass through a sieve, and press with hardness of the tablet is higher but the content uniformity is less. Compress 477-mg tablets using 12-mm punches.

Breast Care Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
20.00	1	Polysorbate 60	20.00
70.00	2	Cetyl alcohol	70.00
60.00	3	Mineral oil (70 cS)	60.00
40.00	4	Glyceryl stearate	40.00
QS	5	Deionized water	QS
QS	6	Preservative	QS

MANUFACTURING DIRECTIONS

Heat oil and water phases separately at 65 to 70°C. Add water phase to oil phase while stirring. Stir to cool. Fill at 20°C. Only food-grade materials should be used in this preparation. Do not use unapproved preservatives.

Bromhexine Hydrochloride Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Quantity/L (g)
4.00	1	Bromhexine HCl	0.80
1000.00	2	Glycerin (glycerol)	200.00
10.00	3	Benzoic acid	2.00
1.70	4	All fruits flavor	0.34
5.00	5	Tartaric acid	1.00
151.58	6	Alcohol (ethanol, 95%)	30.31
2857.00	7	Sorbitol (70% solution)	571.40
10.00	8	Sodium carboxymethyl cellulose (sodium CMC)	2.00
0.72	9	Sodium hydroxide pellets	0.14
QS	10	Purified water	QS to 1 L

MANUFACTURING DIRECTIONS

Add 250.0 g of item 10 to the manufacturing vessel, and heat to 65 to 70°C. Add 20.0 g of item 2 in a separate stainless steel container, and mix item 8 using an Ekato stirrer, carefully avoiding lump formation. Transfer the slurry to the manufacturing vessel and continue mixing to make a clear mucilage. Avoid air entrapment. Cool to 30°C while mixing at slow speed. Transfer the mucilage to container. Load 100.0 g of item 2 to the manufacturing vessel. Add item 6 in a separate stainless steel container, and dissolve item 3 using stirrer. Add 60.0 g of item 2 to the container while mixing at slow speed. Add and dissolve item 1 to the container while mixing at slow speed. Avoid splashing of the solution. Be sure bromhexine is dissolved completely. Add item 4 to the container, and mix well. Transfer the solution to the manufacturing vessel while mixing at high speed. Rinse the container with 20.0 g of item 2, and transfer the rinsing to the manufacturing vessel while mixing. Rinse the container with 20.0 g of item 10, and transfer the rinsing to the manu-

facturing vessel while mixing. Add 15.0 g of item 10 in a separate stainless steel container. Dissolve item 5 using a stirrer, and transfer it to the manufacturing vessel while mixing. Check for clarity of the solution in the manufacturing vessel. The solution must be clear without any undissolved particles of the drug. Add item 7 to the manufacturing vessel while mixing at high speed. Transfer the cooled mucilage of item 8 to the manufacturing vessel used above while mixing at slow speed. Check and record the pH of the solution (limit: 3.3 to 3.6). Dissolve item 9 in 5.0 g of cooled item 10 (30°C) in a separate stainless steel container. Adjust the pH of the syrup in the manufacturing vessel using the sodium hydroxide solution. Add sodium hydroxide solution, small portions at a time. Mix well, and check the pH after every addition. Adjust the pH to 3.5 (limit: 3.3 to 3.6). Bring the volume up to 1.0 L with item 10, and finally mix for 15 to 20 minutes at high speed. Check and record the pH (limit: 3.3 to 3.6). Filter the syrup at 1.5 bar. Recirculate.

Bromhexine Hydrochloride Syrup, Alcohol Free

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Quantity/L (g)
4.00	1	Bromhexine HCl	0.80
1000.00	2	Glycerin (glycerol)	200.00
12.00	3	Sodium benzoate	2.40
1.70	4	All fruit flavor	0.34
17.00	5	Tartaric acid	3.40
2250.00	6	Sorbitol (70% solution)	450.00
10.00	7	Sodium carboxymethyl cellulose (sodium CMC)	2.00
QS	8	Purified water	QS to 1 L

MANUFACTURING DIRECTIONS

Add 240.0 g of item 8 (25°C) to the manufacturing vessel. Add item 5 and mix for 20 minutes at high speed. Load 180.0 g of item 2 into the manufacturing vessel, and mix for 3 minutes. Add item 1 to the manufacturing vessel, and mix for 30 minutes at high speed. Add 20.0 g of item 2 in a suitable vessel, and levigate item 7 using stirrer, carefully avoiding lump formation. Add 40.0 g of item 8 (70°C) to the stainless steel container while mixing to make a clear mucilage; mix for 15 minutes. Avoid air entrapment. Cool down to 25 to 30°C while mixing at slow speed. Transfer the mucilage to the manufacturing vessel. Rinse the vessel with 10.0 g of item 8, and transfer

to the manufacturing vessel. Mix at slow speed for 20 minutes. Transfer item 6 to the manufacturing vessel while mixing. Mix at low speed for 5 minutes. Add 20.0 g of item 8 (25°C) in a separate stainless steel container, and dissolve item 3 using an Ekato stirrer until a clear solution is obtained. Transfer this solution to the manufacturing vessel, and mix at low speed for 3 minutes. Add item 4 to the manufacturing vessel, and mix at low speed for 3 minutes. Record the pH of the solution (limit: 3.3 to 3.7). Adjust the pH of the solution with a 10% solution of sodium hydroxide, if required. Make the volume up to 1 L with item 8 (25°C), and finally mix for 15 to 20 minutes at high speed. Filter the syrup at 1.5 bar. Recirculate.

Bromhexine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
8.00	1	Bromhexine HCl	8.00
78.00	2	Lactose monohydrate	78.00
30.40	3	Corn starch	30.40
3.00	4	Gelatin (powder)	3.00
QS	5	Purified water	12.00
0.60	6	Magnesium stearate	0.60

MANUFACTURING DIRECTIONS

The binding solution is susceptible to microbiological growth, so prepare the solution directly before the granulation process. Protect bromhexine HCl from light. Make slurry in a separate container by dissolving item 4 in hot item 5 (70 to 80°C). Mix for 10 minutes using stirrer at medium speed. Pass items 2, 1, and 3 through a 630-µm sieve using a sifter. Charge the sieved material into the mixer. Mix, using mixer and chopper, for 5 minutes at high speed. Add binding solution to the dry powders in the mixer while mixing at low speed. After the addition is complete, mix for an additional 4 minutes at low speed or until a satisfactory mass is obtained. Spread the wet

granules onto the trays. Load the trolleys into the drying oven. Dry the granules at 60°C for 10 hours. Turn the granules after 4 hours of drying in order to obtain uniform drying. Transfer the dried granules in stainless steel drums. Check moisture content (limit: NMT 2.0%). Pass the dried granules first through a 1.5-mm and then a 1.0-mm sieve using a granulator. Collect in stainless steel drums. Load the granules into the blender. Pass item 6 through a 250-µm sieve using a sifter, and add to the granules in blender; blend for 2 minutes. Compress the granules using a rotary tabletting machine. Use a 7-mm flat, beveled edge punch to compress 1.20 g per tablet at a hardness of NLT 3.0 kp.

Burn Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
120.00	1	Glyceryl stearate SE (Monthybase)	120.00
80.00	2	Myristate octyldodecyl (MOD)	80.00
20.00	3	Apricol kernel oil PEG-6 esters (Labrafil® M1944CS)	20.00
0.50	4	Sodium methylparaben	0.50
0.50	5	Sodium propylparaben	0.50
0.50	6	Sorbic acid	0.50
767.50	7	Deionized water	767.50
10.00	8	Avocado oil	10.00
1.00	9	Fragrance	1.00

MANUFACTURING DIRECTIONS

Mix and heat items 1 to 7 to 75°C. Cool slowly with stirring. At 30°C, add item 8 and then item 9.

Burn Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
15.00	1	Magnesium aluminum silicate (Veegum®)	15.00
568.00	2	Deionized water	568.00
30.00	3	Propylene glycol	30.00
2.00	4	Dimethecone emulsion	2.00
100.00	5	Mineral oil, light	100.00
170.00	6	Acetylated lanolin alcohol	170.00
50.00	7	Benzocaine, USP	50.00
30.00	8	C18–C36 acid	30.00
120.00	9	Glyceryl stearate and PEG-100 stearate	120.00
5.00	10	Polysorbate 60	5.00
QS	11	Preservatives	QS

MANUFACTURING DIRECTIONS

Slowly add item 1 to water, agitating with extensive shear force until smooth. Add items 3 and 4, and heat to 75 to

80°C. Mix and heat items 5 to 11, keeping item 7 suspended to 75 to 80°C; mix the two parts while cooling; pour and fill at 40°C.

Caffeine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
150.00	1	Caffeine powder	150.00
36.00	2	Cellulose (microcrystalline) (Avicel™ PH-102)	36.00
46.00	3	Anhydrous lactose	46.00
48.50	4	Di-Pac granular	48.50
3.00	5	Croscarmellose sodium (Ac-Di-Sol SD-711)	3.00
1.50	6	Fumed silica	1.50
0.75	7	Stearic acid	0.75
0.75	8	Magnesium stearate	0.75
1.20	9	Flavor	1.20

MANUFACTURING DIRECTIONS

Screen items 1, 7, and 8 separately through a 40-mesh sieve. Blend items 1 to 6 and 9 in a V-blender, and mix for 3 minutes. Add item 8 to the blender, and mix for

another 5 minutes. Compress, using 7 kg pressure and 3/8-inch, flat, beveled-edge punches to produce tablets with an average weight of 311 mg.

Calamine Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
80.00	1	Polawax GP200	80.00
10.00	2	Polysorbate 60	10.00
50.00	3	Caprylic/capric triglyceride	50.00
QS	4	Deionized water	QS to 1 kg
100.00	5	Witch hazel distillate	100.00
50.00	6	Glycerin	50.00
20.00	7	Zinc oxide	20.00
20.00	8	Calamine	20.00
QS	9	Preservative, color	QS

MANUFACTURING DIRECTIONS

Heat oil and water phases separately to 65 to 70°C. Add water phase to oil phase while stirring. Add zinc oxide and calamine under high shear. Stir to cool.

Calamine Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
20.00	1	Cellulose (microcrystalline) (Avicel™ RC-591)	20.00
100.00	2	Glycerin	100.00
1.80	3	Methylparaben	1.80
0.20	4	Propylparaben	0.20
100.00	5	Glyceryl stearate and PEG-100 stearate	100.00
25.00	6	Cetyl alcohol	25.00
50.00	7	Zinc oxide	50.00
50.00	8	Calamine	50.00
653.00	9	Distilled water	653.00

MANUFACTURING DIRECTIONS

Mix item 2 with item 9, and heat to 75°C. Add items 3 and 4; mix until dissolved using a shearing mixer. Maintain temperature at 75°C, and gradually add item 1, continue mixing at 75°C for 15 minutes, or until item 1 is homogeneously dispersed. Mix well. When temperature

drops to 60 to 65°C, gradually add items 7 and 8; mix well until powders are homogeneously dispersed. Pass through homogenizer, if necessary; adjust theoretical weight with warm distilled water, and continue mixing until the cream congeals.

Calamine Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
78.30	1	Calamine	78.30
78.30	2	Zinc oxide	78.30
19.60	3	Glycerin	19.60
230.80	4	Deionized water	230.80
558.00	5	Calcium hydroxide solution	558.00
34.40	6	Purified bentonite (Polargel®, NF)	34.40
0.60	7	Carboxymethyl cellulose	0.60

MANUFACTURING DIRECTIONS

Prepare a saturated solution of item 5 by putting 3 g of item 5 in 1000 mL of purified water; mix vigorously for 1 hour. Decant the clear, supernatant liquid for use in the formula. Add the balance of water. Add items 6 and 7 to

this solution with rapid mixing; continue mixing for 15 minutes. In a separate vessel, blend items 1 and 2. Add item 3, and mix until uniform. Begin adding the aqueous solution with mixing until it is blended into a lotion.

Calcium and Vitamin D Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Anhydrous calcium phosphate (dibasic)	500.00
133 IU	2	Vitamin D (as vitamin D3) (3.33 µg/tablet)	3.33 mg
15.00	3	Starch (pregelatinized, NF)	15.00
55.00	4	Cellulose (microcrystalline, NF)	55.00
6.00	5	Magnesium stearate, NF	6.00
5.00	6	Talc (powder), USP	5.00
12.00	7	Wax (hydrogenated vegetable oil) (Sterotex K)	12.00
15.50	8	Sodium starch glycolate, NF	15.50

MANUFACTURING DIRECTIONS

Charge one half of the dibasic calcium phosphate through a mesh screen into a blender. Premix by hand the pregelatinized starch with vitamin D3 beadlets in a suitable container, and sift through a mesh screen into the blender. Charge the microcrystalline cellulose and the remaining calcium phosphate through a mesh screen into the blender.

Mix for 20 minutes. Discharge approximately one third of the granulation into polyethylene-lined drums. Mix the magnesium stearate, talc, hydrogenated vegetable oil wax, and sodium starch glycolate. Mill through a #40 mesh screen into the blender. Return granulation from step above to the blender. Blend together. Compress.

Calcium Carbonate and Glycine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Calcium carbonate (precipitated)	400.00
200.00	2	Glycine (aminoacetic acid)	200.00
QS	3	Starch	QS
6.50	4	Mineral oil (light)	6.50
QS	5	Purified water	QS

MANUFACTURING DIRECTIONS

Add starch to a planetary mixer, and add ten times the quantity of purified water. Heat to boil with constant stirring until a thick, translucent white paste is formed. Use this paste in granulation. Charge calcium carbonate and glycine in a sigma-blade or a planetary mixer, and mix for 10 minutes. Granulate this powder with the starch paste until a suitable mass is obtained. Force the wet mass through a #12-mesh screen onto dryer trays. Dry in an air-

forced oven at 130°F to 140°F or in a fluid-bed dryer. Pass the dried granules through a #12-mesh screen, then through a #18-mesh screen. Pass the granules over a 30-mesh screen, remove the portion passing through the screen, and regranulate. Charge the particles retained on 30-mesh screen in a tumble mixer, add mineral oil, and mix for 8 minutes. Compress 640-mg tablets using 7/16-inch punches.

Calcium Carbonate and Vitamin D Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
600.00	1	Calcium (elemental); use calcium carbonate (90%) for direct compression	1665.00
0.235	2	Vitamin D3 (200.00 IU); use vitamin D3 beadlets	0.282
4.16	3	Magnesium stearate	4.16
83.25	4	Sodium starch glycolate	83.25

MANUFACTURING DIRECTIONS

Make a premix of vitamin D3 successively in three portions of calcium carbonate (total amount equivalent to ~3% of total calcium carbonate), using the geometric dilution. Mix for 10 minutes each time (total: 30 minutes). Add the premix to the sodium starch glycolate. Mix for 10 minutes. Set the blend aside, protected from light, until the next step. Pass the magnesium stearate through a 420 micron aperture screen, if required, and blend it with

another portion of calcium carbonate (~10% of total calcium carbonate). Mix for 5 minutes. Set aside. Add the blended material to the balance of the calcium carbonate. Mix for 10 minutes. Add the premix to blend from above. Mix for 5 minutes. Compress on specially shaped, 0.8100 × 0.3700-inch, ovaloid, bisected punches with a monogram on one side. Theoretical weight of 10 tablets = 17.527 g. Coat using one of the HPMC formulae (see appendix).

Calcium Carbonate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Calcium carbonate (precipitated)	500.00
65.00	2	Kollidon® 30	65.00
97.00	3	Water	97.00
32.00	4	Kollidon® CL	32.00
53.00	5	Ludipress®	53.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 and 2 with the water (item 3), pass through a 0.8 mm sieve, mix the dry granules with items 4 and 5, and press with low compression force. Fill 656 mg in 12-mm planar punches.

Calcium D-Pantothenate Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
600.00	1	Calcium D-pantothenate (BASF)	610.00
150.00	2	Sorbitol (crystalline)	150.00
140.00	3	Avicel™ PH101	140.00
30.00	4	Kollidon® CL	30.00
50.00	5	PEG-6000 (powder)	50.00
QS	6	Flavors	QS

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with low compression force. Compress 987-mg tablets in 12-mm biplanar punches. (Kollidon® CL may be omitted and the tablet weight adjusted.)

Calcium D-Pantothenate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Calcium D-pantothenate (BASF)	100.00
150.00	2	Ludipress®	150.00
10.00	3	Kollidon®	10.00
3.00	4	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press into 252-mg tablets using medium compression force and biplanar 8-mm punches.

Calcium D-Pantothenate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
280.00	1	Calcium D-pantothenate (BASF)	285.00
50.00	2	Avicel™ PH101	50.00
150.00	3	Dibasic calcium phosphate	150.00
20.00	4	Kollidon® CL	20.00
3.00	5	Stearic acid	3.00
3.00	6	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press into 518-mg tablets using medium compression force and 12-mm biplanar punches.

Calcium Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
634.00	1	Calcium lactate	634.00
610.00	2	Calcium gluconate	610.00
185.21	3	Calcium carbonate	185.21
400.00	4	Sodium bicarbonate	400.00
468.25	5	Tartaric acid	468.25
46.25	6	Povidone (Kollidon® 30)	46.25
11.75	7	Povidone (Kollidon® 30)	11.75
QS	8	Isopropyl or ethyl alcohol (96%)	QS
97.50	9	Crospovidone (Kollidon® CL)	97.50
46.25	10	PEG-6000	46.25
QS	11	Flavor	QS

MANUFACTURING DIRECTIONS

Granulate items 1 to 6 in a solution of items 7 and 8; dry, sieve, and mix well with items 9 to 11. Compress at low pressure to form 2.5-g tablets, 20 mm in diameter.

Calcium Gluconate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
350.00	1	Calcium gluconate (powder)	360.00
117.00	2	Lactose monohydrate	117.00
11.00	3	Kollidon® 30	11.00
QS	4	Isopropanol	90.00
25.00	5	Kollidon® CL	25.00
2.00	6	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 3 with item 4; dry, pass through an 0.8-mm sieve, and mix with items 5 and 6. Press into 500-mg tablets using high compression force and 12-mm biplanar punches.

Calcium Glycerophosphate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Calcium glycerophosphate	500.00
117.50	2	Corn starch	117.50
15.00	3	Kollidon® 90 F	15.00
60.00	4	Water	60.00
15.00	5	Kollidon® CL	15.00
2.50	6	Magnesium stearate	2.50

MANUFACTURING DIRECTIONS

Granulate items 1 to 3 with item 4; dry, sieve, and mix with items 5 and 6. Press into 650-mg tablets using medium to high compression force and 12-mm biplanar punches.

Calcium Glycerophosphate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Calcium glycerophosphate	200.00
297.50	2	Ludipress®	297.50
2.50	3	Magnesium stearate	2.50
QS	4	Aerosil® 200	QS

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, and mix. Press into 470-mg tablets using high compression force and 12-mm biplanar punches.

Calcium Iodide and Ascorbic Acid Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
311.60	1	Glucose liquid (corn syrup)	311.60
53.90	2	Glycerin (96%)	53.90
30.00	3	Anhydrous calcium iodide; use calcium iodide solution 27% w/w	111.11
1.00	4	Ascorbic acid (white powder)	1.00
485.30	5	Sucrose (granulated sugar)	485.30
0.80	6	Saccharin sodium (powder) ^a	0.80
8.00	7	Sodium cyclamate (XIII powder)	8.00
1.31	8	Honey artificial flavor, AU-73	1.31
0.33	9	Floral mint artificial flavor	0.33
51.53	10	Alcohol (ethanol; 190 proof)	51.53
0.60	11	Isoproterenol sulfate (powder)	0.60
0.05	12	FD&C Yellow Dye No. 5	0.05
0.25	13	Caramel (acid proof)	0.25
QS	14	Water purified	~344.0 mL

^a Use 1.2 g of saccharin to replace cyclamate; adjust balance with sucrose.

MANUFACTURING DIRECTIONS

Isoproterenol is toxic; wear a dust mask, and avoid contact. The product is sensitive to oxidation. Manufacture under N₂ protection, and protect product from light and heat; all water must be boiled, cooled, and gassed with nitrogen. Load glucose and glycerin into a suitable mixing tank. Add 187 mL purified water to tank with mixing. Begin bubbling N₂ protection for the balance of the process. Add and dissolve saccharin sodium and sodium cyclamate, if used, with mixing. Add calcium iodide to the tank with good mixing. Add and dissolve ascorbic acid

and sugar. Dissolve the flavors in alcohol, and add with mixing to the main batch. Dissolve isoproterenol in 10 to 13 mL of water and add, with mixing, to the main batch. Dissolve dye in 3.5 mL purified water, and add solution to tank with mixing. (*Note:* Dye may be deleted.) Add caramel with mixing to main batch. Move N₂ source from the bottom to the top of the tank. Turn off mixer. Allow to stand overnight under N₂ protection to let entrapped gases escape. QS to 1 L. Mix for 1 hour. Filter and circulate product through a suitable filter press until sparkling clear.

Calcium Phosphate Tablets for Cats and Dogs (Direct Compression)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Dicalcium phosphate	400.00
100.00	2	Wheaten flour	100.00
1.00	3	Citric acid crystalline	1.00
272.00	4	Lactose monohydrate	272.00
QS	5	Flavors	QS
20.00	6	Kollidon® 90 F	20.00
4.00	7	Magnesium stearate	4.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with medium to high compression force (20 kN).

Compress into 800-mg tablets using 12-mm biplanar punches.

Calcium Phosphate Tablets for Cats and Dogs

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Dicalcium phosphate	400.00
100.00	2	Wheaten flour	100.00
1.00	3	Citric acid crystalline	1.00
262.00	4	Lactose monohydrate	262.00
QS	5	Flavors	QS
30.00	6	Kollidon® 30 F	30.00
150.00	7	Water	150.00 mL
4.00	8	Magnesium stearate	4.00

MANUFACTURING DIRECTIONS

Granulate items 1 to 6 in item 7; dry, add item 8, and pass through an 0.8-mm sieve. Compress 800-mg tablets using 12-mm biplanar punches.

Carbinoxamine Maleate, Phenylpropanolamine, and Acetaminophen Sustained-Release Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Cabinoxamine maleate	5.00
75.00	2	Phenylpropanolamine hydrochloride	75.00
50.00	3	Acetaminophen	50.00
143.35	4	Sucrose and maize starch microgranules	143.35
6.34	5	Polyvidone (PVP)	6.34
0.01	6	Dye	0.01
0.075	7	Dye	0.075
0.025	8	Dye	0.025
23.99	9	Talc	23.99

MANUFACTURING DIRECTIONS

This product requires separate preparation of microgranules for each active ingredient. This preparation requires a coating pan equipped with air suction and hot air heating system, mixer, automatic airless pump with a spray gun, vibrating sieve, and capsule-filling machine with triple-feed microgranular system. Place the neutral microgranules in the coating pan; prepare a 20% solution of PVP. Maintain the temperature of microgranules at $20 \pm 2^{\circ}\text{C}$. Using the pump, apply the solution of PVP, then project the active ingredient onto the microgranules with a plastic

scoop until they are dry. Repeat these operations until all the active ingredients have been incorporated. Sieve the microgranules with a 1.11-mm sieve. Dry the microgranules at $30 \pm 5^{\circ}\text{C}$ for 3 hours. Prepare a 40% solution of shellac in alcohol and the required quantity of talc. Apply the shellac solution, maintaining a microgranule temperature of $20 \pm 2^{\circ}\text{C}$, and add the talc simultaneously. Sieve the microgranules through a 1.18-mm sieve. Dry the microgranules at 18 to 23°C for 8 hours. Store until used. Test for dissolution and rework if necessary.

Carbonyl Iron, Copper Sulfate, and Manganese Sulfate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
24.00	1	Carbonyl iron (BASF)	24.00
0.16	2	Copper sulfate	0.16
3.50	3	Manganese sulfate	3.50
100.00	4	Ludipress	100.00
2.00	5	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

Pass all components through a 0.5-mm sieve, mix, and press into 131-mg tablets using medium compression force and 8-mm biplanar punches.

Carnitine and Coenzyme Q Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
1.00	1	Coenzyme Q 10	1.00
1.00	2	Lutrol E 400	1.00
4.00	3	Cremophor RH 40	4.00
QS	4	Preservative	QS
QS	5	Water	QS to 1 L
40.00	6	Carnitine	40.00

MANUFACTURING DIRECTIONS

Heat the mixture of items 1 to 5 to 60°C, stir well. Cool to room temperature, and add and dissolve item 6.

Cetrimide Antiseptic Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
50.00	1	Cetearyl alcohol and cetrimonium bromide	50.00
75.00	2	White petroleum jelly	75.00
60.00	3	Mineral oil (70 cS)	60.00
QS	4	Deionized water	QS to 1 kg
QS	5	Perfume, preservative, color	QS

MANUFACTURING DIRECTIONS

Heat oil and water phases separately to 60 to 65°C. Add the water phase to the oil phase while stirring. Stir to cool.

Charcoal Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Activated charcoal	250.00
150.00	2	Bolus alba (Merck)	150.00
28.00	3	Kollidon® 25	28.00
38.00	4	Acacia gum	38.00
QS	5	Water + isopropanol (10 + 3)	575.00 mL
15.00	6	Cremophor EL	15.00
QS	7	Isopropanol	300.00 mL

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 4 with item 5, and pass through a 1-mm sieve. Dry until a relative powder humidity of 90% is reached. Add solution of items 6 and 7, and

pass again through a 0.8 mm sieve. Dry the granules, and press into 481-mg tablets using low compression force and 12-mm planar punches. Dry the obtained tablets.

Chlophedianol, Ipecac, Ephedrine, Ammonium Chloride, Carbinoxamine, and Balsam Tolu Syrup

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/L (g)
0.001 mL	1	Ipecac fluid extract	1.00 mL
5.00	2	Chlophedianol hydrochloride	5.00
1.32	3	Ephedrine hydrochloride (powder)	1.32
8.80	4	Ammonium chloride (reagent-grade granules)	8.80
0.80	5	Carbinoxamine maleate	0.80
0.90	6	Methyl paraben	0.90
0.10	7	Propyl paraben	0.10
6.25	8	Balsam of Tolu (eq. aqueous extract)	6.25
2.66	9	Saccharin sodium (dihydrate powder)	2.66
319.22	10	Sucrose (granulated sugar)	319.22
238.33	11	Glucose liquid (corn syrup)	238.33
83.93	12	Sorbitol solution (calculate as 70% sorbitol crystals)	83.93
40.00	13	Alcohol	40.00
166.67	14	FD&C Red Dye (Amaranth E123)	166.67 mg
0.80	15	Raspberry flavor	0.80
100.00	16	Propylene glycol	100.00
QS	17	HyFlo filter aid	0.50
QS	18	Water purified	~450.00 mL

MANUFACTURING DIRECTIONS

Charge Balsam of Tolu and 25 mL of water in a steam bath. Raise the temperature, stirring continuously in order to mix water with the balsam. Boil for half an hour, and allow to decant while cooling. Discard extracted Balsam of Tolu. Filter the supernatant liquid through filter paper, and store apart. Charge 150 mL water in a jacketed mixing tank, and heat to boiling. Add and dissolve parabens with mixing. Add and dissolve sugar with constant mixing. Heat to 70 to 75°C. Once sugar is dissolved, add glucose, sorbitol, and saccharin sodium. Mix well until dissolved. Dissolve ammonium chloride in 28 mL water. Add to mixing tank. Add extract Balsam of Tolu from first step

with mixing. Mix well and cool to 25 to 30°C. Add and dissolve ephedrine and carbinoxamine in 20 mL water, and add to mixing tank. Mix well. Add and dissolve chlophedianol in 50 g of propylene glycol, and add to mixing tank. Add balance of propylene glycol to mixing tank. Add and dissolve Ipecac fluid extract and raspberry flavor in alcohol. Add to mixing tank. Dissolve dye in 5 mL water, and add to tank with continuous mixing. Rinse container with 5 mL of water, and add rinsing. Adjust to volume with purified water. Add HyFlo filter aid to syrup, and mix well. Recirculate through filter press or equivalent until sparkling clear.

Chlorhexidine Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
20.00	1	Chlorhexidin diacetate	20.00
300.00	2	1,2-Propylene glycol (Pharma)	300.00
220.00	3	Lutrol F 127	220.00
460.00	4	Water	460.00

MANUFACTURING DIRECTIONS

Dissolve chlorhexidin diacetate in propylene glycol at >70°C. Stir well, and slowly add Lutrol F 127 and water.

Maintain the temperature until the air bubbles escape. A clear, colorless gel is obtained.

Chlorhexidine Lozenges

Bill of Materials			
Scale (mg/lozenge)	Item	Material Name	Quantity/1000 lozenges (g)
5.00	1	Chlorhexidine	5.00
150.00	2	Sorbitol (crystalline)	150.00
5.00	3	Kollidon® VA 64	5.00
5.00	4	Menthol (crystalline)	5.00
5.00	5	Eucalyptol (crystalline)	5.00
1.00	6	Aspartame, potassium	1.00
0.10	7	Saccharin sodium	0.10
2.00	8	Aerosil® 200	2.00
1.00	9	Magnesium stearate	1.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with medium compression force. Compress into 175-mg lozenge using 8-mm biplanar punches.

Chlorpheniramine Maleate Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Quantity/L (g)
2.00	1	Chlorpheniramine maleate	0.40
3000.00	2	Sucrose	600.00
4.50	3	Methyl paraben	0.90
1.50	4	Propyl paraben	0.30
1.00	5	Citric acid (monohydrate)	0.20
2.40	6	Sodium citrate	0.48
2.00	7	Green banana flavor	0.40
—	8	Purified water	QS to 1 L

MANUFACTURING DIRECTIONS

Add 500.0 g of purified water to the manufacturing vessel, and heat to 95 to 98°C. Add items 3 and 4 while mixing to dissolve at high speed. Mix for 5 minutes. Add item 2 while mixing at slow speed. Maintain a temperature of 95 to 98°C. Mix for 1 hour at high speed. Cool down to 30°C while mixing at slow speed. Dissolve items 5 and 6 in 20.0 g of cooled purified water (25°C). Transfer the solution to the manufacturing vessel while mixing at high speed. Mix for 2 minutes. Add 8.0 g of cold purified water (25 to 30°C) in a separate container, and dissolve item 1

by using stirrer. Mix for 10 minutes and transfer to the manufacturing vessel. Rinse the container with 2.0 g of cooled purified water (25°C), and transfer the rinsings to the manufacturing vessel while mixing at high speed. Add item 7 to the manufacturing vessel while mixing. Mix for 10 minutes at high speed. Bring the volume up to 1 L with purified water, and finally mix for 15 to 20 minutes at high speed. Check and record the pH (limit 5.0 to 5.2 at 25°C). If required, adjust pH with 10% citric acid or 10% sodium citrate solution. Filter the syrup at 1.5 bar. Bubble the syrup with nitrogen gas.

Chymotrypsine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
27.00	1	Chymotrypsine	27.50
71.50	2	Ludipress®	71.50
1.00	3	Magnesium stearate	1.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm screen, and press with low compression force. Compress into 100-mg tablets using 8-mm biplanar punches.

Citrate Effervescent Powder

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/kg (g)
0.50	1	Oil lemon terpeneless	0.50
10.00	2	Lemon flavor (natural microseal)	10.00
QS	3	Alcohol dehydrated (absolute, doubly rectified)	6.50
440.33	4	Sodium bicarbonate	440.33
0.35	5	Saccharin sodium	0.35
157.50	6	Anhydrous sodium citrate	157.50
178.82	7	Anhydrous citric acid (powder)	178.82
222.50	8	Acid tartaric	222.50

MANUFACTURING DIRECTIONS

All processing should be done in controlled humidity at a maximum relative humidity of 40% at 25°C. Sodium citrate and citric acid are anhydrous. Dissolve lemon oil in dehydrated alcohol with stirring in a suitable container (delete this step if using powdered lemon flavor). Sift sodium bicarbonate, if necessary, through a 595-μm screen. Charge into a suitable mixer, and mix for 10 minutes. Very slowly add solution from first step to the mixer while mixing; continue mixing for at least 10 minutes and up to a total of 30 minutes, depending on equipment. Screen the massed granulation mixture through a 595-μm screen, and divide approximately in half. Premix saccharin sodium into sodium citrate (and

lemon powder, if used), and sift through a 595-μm screen or mill fitted with a 595-μm screen (knives forward, medium speed). Sift both citric acid and tartaric acid separately through a 595-μm screen or mill separately using a comminuting mill with a 595-μm aperture (knives forward, medium speed). Load materials into a suitable blender, preferably in the following order: milled tartaric acid, milled citric acid, half of granulation mixture, milled saccharin sodium, sodium citrate, and remaining granulation mixture. Blend for 20 minutes, and pack into double plastic bags inside fiber drums. Provide silica gel protection to maintain low humidity in drums. If blended material is lumpy, pass through a 1.2-mm screen before bagging.

Crospovidone Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1000.00	1	Crospovidone (micronized)	1000.00
150.00	2	Citric acid	150.00
25.00	3	Aerosil® 200	25.00
100.00	4	Sucrose (crystalline)	100.00
1.00	5	Saccharin sodium	1.00
QS	6	Water	QS
5.00	7	Magnesium stearate	5.00
125.00	8	Sodium bicarbonate	125.00
65.00	9	Flavor mixture	65.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 5 with item 6, dry, and pass through a sieve. Mix the dry granules with items 7 to 9, and press with medium compression force. The dosage may be

increased to 2000 mg crospovidone by increasing the tablet weight to 3200 mg. Compress 1590-mg tablets using 20-mm diameter biplanar punches.

Crospovidone Water Dispersible Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1000.00	1	Crospovidone M (BASF)	1000.00
50.00	2	Aerosil® 200	50.00
250.00	3	Sucrose (crystalline)	250.00
5.00	4	Saccharin sodium	5.00
2.00–3.00	5	Flavors	2.00–3.00
380.00	6	Water	380.00
5.00	7	Magnesium stearate	5.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 5 with item 6, dry, and pass through a sieve. Mix the dry granules with item 7, and press with low compression force. The dosage may

be increased to 2000 mg Crospovidone by increasing the tablet weight to 2600 mg. Compress 1280-mg tablets using 20 mm biplanar punches.

Cyanocobalamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00 ug	1	Cyanocobalamin; use gelatin-coated cyanocobalamin (0.1%)	50.00
150.00	2	Ludipress®	150.00
1.50	3	Magnesium stearate	1.50
2.00	4	Sicovit Quinoline lake, yellow	2.00
3.00	5	Sicovit Yellow lake, orange	3.00

MANUFACTURING DIRECTIONS

Prepare a premix of item 1 and 2, and add to items 3 to 5. Pass through a 0.5-mm sieve, and press with low compression force. Compress into 209-mg tablets using 8-mm biplanar punches.

Dexpanthenol Gel-Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
50.00	1	Dexpanthenol (BASF)	50.00
100.00	2	Liquid paraffin	100.00
150.00	3	Lutrol E 400	150.00
180.00	4	Lutrol F 127	180.00
QS	5	Water	QS to 1 kg

MANUFACTURING DIRECTIONS

Dissolve dexpanthenol and Lutrol E 400 in water, add liquid paraffin, and stir, heating to 60 to 70°C. Slowly add Lutrol F 127, and stir until dissolved. Cool to room temperature, stirring continuously until the air bubbles disappear.

Dextromethorphan, Pseudoephedrine, and Chlorpheniramine Maleate Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
2.00	1	Dextromethorphan hydrobromide	2.00
4.00	2	<i>d</i> -Pseudoephedrine hydrochloride	4.00
0.40	3	Chlorpheniramine maleate	0.40
25.00	4	Sorbitol syrup	25.00
0.20	5	Saccharin sodium	0.20
3.00	6	Hydroxyethyl cellulose (Natrosol®)	3.00
2.50	7	Sodium benzoate	2.50
1.05	8	Banana flavor	1.05
1.10	9	Custard flavor	1.10
1.20	10	Trisodium citrate dihydrate (powder)	1.20
QS	11	Deionized water	QL 1L

MANUFACTURING DIRECTIONS

In a suitable stainless steel vessel, combine sorbitol syrup, hydroxyethylcellulose, and deionized water; mix well. Add sodium benzoate, and stir again for 5 minutes. After obtaining a clear solution, stir the hydroxyethyl cellulose suspension, rinse the container with deionized water, and transfer the rinsings to the vessel. Heat the vessel to 40 to 50°C, and stir the mix for 1 hour. After 1 hour, a clear gel without lumps is obtained. Dilute the gel with sorbitol syrup, and cool to 30°C. In a separate vessel, add deionized water, and heat while stirring to 50°C. After reaching this temperature, dissolve, in this order, dextromethorphan hydrobromide, chlorpheniramine maleate, and pseudoephedrine hydrochloride and saccharin sodium. Cool the solution to 25°C. In a suitable stainless steel container, add deionized water and while stirring dissolve trisodium

citrate under 0.6-bar vacuum and high speed. Transfer the active substance solution to the syrup vehicle. Rinse the vessel twice with deionized water. Add while stirring (low) the custard and banana flavors. Mix for 10 minutes. Then, while stirring, add the solution from step above; keep stirring for 15 minutes at moderate speed. Stop stirring and check pH (5.9 to 6.2); adjust with 10% trisodium citrate solution; after each addition, where necessary, stir for 5 minutes before recording pH again. Finally, make up the volume with deionized water, and stir once more for 15 minutes under vacuum (0.6 bar) at moderate speed. Stop stirring and remove vacuum; check final volume once more. Filter the clear syrup under compressed air pressure, first through a filter of 330-μm and then through a 20-μm filter of propylene type.

Dihydroxyaluminum Sodium Carbonate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
31.00	1	Dihydroxyaluminum sodium carbonate (Giulini A 265)	31.00
61.50	2	Sugar	61.50
2.00	3	Magnesium stearate	2.00
15.00	4	Starch	15.00
QS	5	Flavor, sweetener	0.50

MANUFACTURING DIRECTIONS

Blend to mix and compress 110 mg in 6 mm punch.

Dimenhydrinate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Dimenhydrinate	50.00
245.00	2	Ludipress®	245.00
5.00	3	Magnesium stearate	5.00

MANUFACTURING DIRECTIONS

Mix all components, sieve, and press with low compression force. Compress into 300-mg tablets using 8-mm biplanar punches.

Dimenhydrinate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Dimenhydrinate	50.00
50.00	2	Cellulose (microcrystalline) (Avicel™ PH101)	50.00
125.00	3	Lactose	125.00
2.29	4	Croscarmellose sodium (Ac-Di-Sol, SD-711)	2.29
1.00	5	Fumed silicon dioxide	1.00
0.50	6	Stearic acid	0.50
0.50	7	Magnesium stearate	0.50

MANUFACTURING DIRECTIONS

Screen items 1, 5, and 6 separately through a 40-mesh sieve. Blend items 1, 2, 4, and 5 in a V-blender for 3 minutes. Add item 3 in the blender, and mix for 17 minutes. Add item 6,

and blend for 3 minutes. Add item 7 to the blender, and mix for 5 minutes. Compress using 3/8-inch, flat, beveled-edge punches to a hardness of 6 kp and average tablet weight of 228 mg.

Dimenhydrinate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	I. Dimenhydrinate	100.00
40.00	2	Lactose monohydrate	40.00
40.00	3	Corn starch	40.00
6.00	4	Kollidon® 90 F	6.00
30.00	5	Isopropanol	30.00
14.00	6	Kollidon® CL	14.00
16.00	7	Talc	16.00
2.00	8	Aerosil® 200	2.00
2.00	9	Calcium arachinate	2.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 4 with item 5, dry, pass through an 0.8-mm sieve, mix with items 6 to 9, and press

with low compression force. Compress into 210-mg tablets using 9-mm biconvex punches.

Diphenhydramine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Diphenhydramine hydrochloride	25.00
150.00	2	Calcium phosphate (dibasic)	150.00
20.00	3	Starch (StaRX 1500)	20.00
QS	4	Polyvinylpyrrolidone (PVP)	QS
QS	5	Alcohol, USP	QS
75.00	6	Stearic acid (fine powder)	75.00
25.00	7	Cellulose (microcrystalline)	25.00
QS	8	Purified water, USP	QS

MANUFACTURING DIRECTIONS

In a planetary mixer, charge the diphenhydramine hydrochloride, calcium phosphate dibasic and starch. Mix for 5 to 10 minutes. In a separate mixer, charge polyvinylpyrrolidone, alcohol, and water in the ratio: 1:50:40. Moisten this mixture with solution from the previous step to granulate. Record the volume used. Pass the wet mass through a #14-mesh screen on dryer trays. Dry the granulation at

120 to 130°F or use a fluid-bed dryer. Pass the dried granules through a #20-mesh screen. Charge dried granules to twin-shell blender, and add stearic acid (previously passed through #30-mesh screen) and microcrystalline cellulose. Mix for 5 to 7 minutes. Compress to 300-mg tablets using a rotary press with 5/16-inch standard concave punches.

Econazole Nitrate and Benzoyl Peroxide Anti-Acne Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
200.00	1	PEG-6 and PEG-32 and glyceryl stearate (Tefose® 63)	200.00
30.00	2	Mineral oil	30.00
30.00	3	Apricot kernel oil PEG-6 esters (Labrifil® M 1944)	30.00
0.50	4	Sorbic acid	0.50
0.50	5	Sodium methyl paraben	0.50
724.00	6	Deionized water	724.00
5.00	7	Benzoyl peroxide	5.00
10.00	8	Econazole nitrate	10.00

MANUFACTURING DIRECTIONS

Mix and heat items 1 to 6 together, and bring temperature to 75°C. Allow to cool while stirring. Add items 7 and 8 at 30°C, and mix well until uniform.

Econazole Nitrate and Benzoyl Peroxide Anti-Acne Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
50.00	1	PEG-6 stearate, Cetech-20, and Steareth-20 (Tefose® 2000)	50.00
30.00	2	Mineral oil	30.00
20.00	3	Cetyl alcohol	20.00
0.70	4	Sodium methyl paraben	0.70
0.30	5	Sorbic acid	0.30
884.00	6	Deionized water	884.00
5.00	7	Benzoyl peroxide	5.00
10.00	8	Econazole nitrate	10.00

MANUFACTURING DIRECTIONS

Mix and heat items 1 to 3 together, and bring temperature to 75°C. Allow to cool while stirring. Mix items 4 to 6, and add to above while stirring. Cool with stirring. Add items 7 and 8 at 30°C while stirring.

Eucalyptol Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
80.00	1	Eucalyptol	80.00
40.00	2	Cremophor RH 40	40.00
QS	3	Preservative	QS
QS	4	Water	QS to 1 L

MANUFACTURING DIRECTIONS

Mix eucalyptol and cremophor at 65°C, stir well, and slowly add the warm solution of item 3 to produce a clear or slightly opalescent, colorless liquid.

Eucalyptus and Mint Emulsion

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
427.50	1	Distilled water	427.50
375.00	2	Eucalyptamint	375.00
70.00	3	Sodium stearyl lactylate (Pationic® SSL)	70.00
35.00	4	PEG-20 hydrogenated lanolin (Supersat ANS4)	35.00
17.50	5	Ritasynt IP	17.50
80.00	6	Ceteryl alcohol, Polysorbate 60, PEG-15 stearate, and steareth-20 (Ritachol 1000)	80.00

MANUFACTURING DIRECTIONS

Heat item 1 to 71°C. Combine rest of the ingredients in another container, and heat to 71°C. Slowly add water at 71°C, and mix for 1 hour. Cool the mixture to 35 to 45°C, and fill.

Eucalyptus and Mint Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
160.00	1	Menthol	160.00
40.00	2	Eucalyptus	40.00
800.00	3	Anhydrous lanolin, USP	800.00

MANUFACTURING DIRECTIONS

Mix lanolin until melted (approximately at 50°C), add remaining ingredients, and mix for 1 hour. Fill hot.

Ferrous Fumarate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Ferrous fumarate	200
295.00	2	Ludipress®	295
5.00	3	Magnesium stearate	5

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with low compression force. Compress into 509-mg tablets using 12-mm biplanar punches.

Ferrous Sulfate, Manganese Sulfate, and Copper Sulfate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
65.00	1	Anhydrous ferrous sulfate	65.00
3.50	2	Manganese sulfate	3.50
0.16	3	Copper sulfate	0.16
70.00	4	Ludipress®	70.00
10.00	5	Kollidon® 30	10.00
2.00	6	Magnesium stearate	2.00
3.00	7	Aerosil® 200	3.00

MANUFACTURING DIRECTIONS

Pass all components through a 0.5-mm sieve, mix, and press with high compression force. Compress into 149-mg tablets using 8-mm biplanar punches.

Ferrous Sulfate Oral Solution

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Quantity/L (g)
75.00	1	Ferrous sulfate ^a	125.00
294.00	2	Sucrose	490.00
147.00	3	Maltitol solution (Lycasin® 80/55)	245.00
0.30	4	Citric acid (monohydrate)	0.50
0.90	5	Citric acid (monohydrate)	1.50
0.06	6	FD&C Yellow Dye No. 6 (sunset yellow FCF)	1.00
3.12	7	Guarana flavor 12144-33	5.20
0.33	8	Potassium sorbate	0.55
0.30	9	Saccharin sodium	0.50
—	10	Purified water	QS to 1 L

^a Equivalent to 15 mg iron (Fe).

MANUFACTURING DIRECTIONS

Bubble nitrogen throughout the process. Check and record pH of the purified water (limit: 5.0 to 6.5). Collect 166.67 g of purified water in mixer. Heat to 90 to 95°C for 10 minutes. Add item 8; stir to dissolve to a clear solution. Add item 2; stir to dissolve to a clear solution. Add item 3; stir for 10 minutes, and cool to 30 to 35°C. Dissolve item 4 in 10.0 g of purified water (30 to 35°C), and add to first step. Dissolve item 9 in 10.0 g of purified water (30 to 35°C), and add to first step. Dissolve item 5

in 273.33 g of purified water (30 to 35°C). Then add item 1 to the clear solution, and dissolve slowly without aeration. Add to mixer. Dissolve item 6 in 10.0 g of purified water (25 to 30°C), and add to first step. Add item 7 to first step. Mix at low speed for 10 minutes. Bring volume up to 1.0 L with purified water. Check and record pH (target: 2.20; limit: 1.95 to 5.15). Filter the drops with recirculation. Transfer the filtered drops to a storage vessel under an N₂ blanket. Use the nitrogen blanket in the tank throughout the storage and filling period.

Ferrous Sulfate Oral Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Quantity/L (g)
200.00	1	Ferrous sulfate ^a	40.00
3350.00	2	Sucrose	670.00
750.00	3	Maltitol solution (Lycasin® 80/55)	150.00
4.16	4	Citric acid (monohydrate)	833.20
8.33	5	Citric acid (monohydrate)	1.66
0.50	6	Color	0.10
15.50	7	Flavor	3.10
—	8	Purified water	QSto 1 L

^a Equivalent to 40 mg elemental iron.

MANUFACTURING DIRECTIONS

Bubble nitrogen throughout the process. Heat 300.0 g of purified water to 95°C. Add item 2 while stirring at low speed. Dissolve to clear solution by stirring at 95°C. Add item 3. Stir at low speed and cool to 25 to 30°C. Dissolve item 4 in 17.0 g of item 8, and add to the first step. Dissolve item 5 in 180.0 g of purified water in a separate stainless steel container. Then add item 1 to the clear

solution, and dissolve slowly without aeration. Add to first step. Dissolve item 6 in 16.0 g of purified water, and add to the first step. Add item 7 to the first step. Mix at low speed for 10 minutes. Bring volume up to 1 L with purified water. Check and record pH (limit: 2.0 to 5.0). Filter the syrup at 1.5 bar. Recirculate about 100 to 150 mL of syrup. Use a nitrogen blanket in the tank throughout the storage period.

Ferrous Sulfate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Anhydrous ferrous sulfate	203.00
185.00	2	Ludipress®	185.00
15.00	3	Kollidon® VA 64	15.00
4.00	4	Magnesium stearate	4.00
4.00	5	Talc	4.00
3.00	6	Aerosil® 200	3.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press to tablets with medium compression force. Compress into 413-mg tablets using 8-mm biplanar punches.

Fir Needle Oil Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
30.00	1	Fir needle oil (Frey & Lau)	30.00
50.00	2	Camphora	50.00
60.00	3	Cremophor RH 40	60.00
403.00	4	Ethanol (96%)	403.00
457.00	5	Water	457.00

MANUFACTURING DIRECTIONS

Mix the active ingredients with Cremophor RH 40 and heat to 50 to 60°C. Add the ethanol to the well-stirred

solution, then slowly add the warm water to produce a clear or slightly opalescent liquid. The amount of Cremophor RH 40 required depends on the type of fir needle oil.

Folic Acid Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Folic acid ^a	5.24
12.00	2	Maize starch (dried) ^b	12.00
5.26	3	Cellulose (microcrystalline) (Avicel™ PH102)	5.26
20.00	4	Cellulose (microcrystalline) (Avicel™ PH102)	20.00
1.50	5	Colloidal silicon dioxide (Aerosil® 200)	1.50
66.00	6	Lactose (spray-dried) ^c	66.00
2.50	7	Talc (fine powder)	2.50
2.50	8	Stearic acid (fine powder)	2.50

^a Extra folic acid is added (0.08 mg/tablet) to compensate water (water NMT 8.0%).

^b LOD: NMT 4.5% when dried at 120°C for 4 hours.

^c Meets the USP NF, except particle size distribution, as follows: min. 98%, 250 µm; 30 to 60%, 100 µm; max. 15%, 45 µm.

MANUFACTURING DIRECTIONS

Folic acid must be protected from exposure to direct light. Sift items 1, 2, and 3 through a Fitz mill (impact forward, high speed), and collect in a stainless steel drum. Load the material into a blender, and mix for 3 minutes. Sift items 4 to 8 through a 500-µm sieve using a sifter, and collect in a stainless steel drum. Load this sieved material

into a blender. Mix for 5 minutes. Unload the lubricated powder into a stainless steel drum. Check for small lumps or globules in the powder mix. If required, pass the entire mass through a 500-µm sieve using a sifter, and mix for 1 minute in a blender. Compress into 1.15-g tablets (hardness, 3 to 7 kp) using 7-mm round flat punches. For 1-mg tablets, compensate with lactose and compress as above.

Folic Acid Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Folic acid	5.00
195.00	2	Ludipress®	195.00
1.50	3	Magnesium stearate	1.50

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press into tablets using medium compression force. If the content uniformity does not meet the requirements, prepare

a premix of the active ingredient with a small part of the Ludipress or with lactose monohydrate before mixing with the other components of the formulation. Compress into 213-mg tablets using 8-mm biplanar punches.

Foot Bath

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
200.00	1	Polysorbate 20	200.00
2.50	2	Menthol	2.50
10.00	3	α -Bisabolol	10.00
20.00	4	Disodium undecylenamido MEA-sulfosuccinate	20.00
20.00	5	Perfume (menthol compatible)	20.00
QS	6	Deionized water	QS to 1 L
QS	7	Preservative, color	QS

MANUFACTURING DIRECTIONS

Predissolve menthol, α -bisabolol, and perfume in Polysorbate 20. Add mixture to the water phase while stirring. Stir until homogeneous, and then fill.

Foot Freshener Cream

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/L (g)
30.00	1	Alcohol and Cetareth-20 (Cosmowax® EM5483)	30.00
30.00	2	Isopropyl Myristate (Crodamol® IPM)	30.00
5.00	3	Cetyl esters (Crodamol® SS)	5.00
20.00	4	Oleyl alcohol	20.00
5.00	5	Propylene glycol	5.00
5.00	6	Carbopol® 980	5.00
QS	7	Deionized water	QS to 1 L
300.00	8	Ethanol (DEB100)	300.00
2.00	9	Triclosan (Irgasan® DP300)	2.00
0.50	10	Menthol	0.50
4.00	11	Triethanolamine 99 (to give pH 6.0 to 7.0)	~4.00

MANUFACTURING DIRECTIONS

Preblend ethanol, Irgasan, and menthol and warm to 50°C. Heat water and oil phases separately to 70°C. Add the

water phase to the oil phase while stirring. Stir to cool, adding the preblend at 60°C; adjust pH.

Foot Mousse

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
300.00	1	Ethanol (DEB100)	300.00
1.00	2	Menthol	1.00
QS	3	Deionized water	QS
20.00	4	Undecyleneamide DEA and diethanolamine	20.00
5.00	5	Cetrimonium bromide	5.00
10.00	6	PEG-75 and water	10.00
QS	7	Perfume, preservative, color	QS

MANUFACTURING DIRECTIONS

Dissolve menthol in ethanol. Add remaining ingredients. Pack into mechanical mousse applicator, such as the

Kunststoff AG Supermatic foamer system, Airspray International BV jet foamers, or Calmar foamers.

Garlic Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
95.00	1	Calcium phosphate, dibasic	95.00
94.00	2	Lactose monohydrate	94.00
9.00	3	Kollidon® 30	9.00
25.00	4	Water	25.00
100.00	5	Dried garlic powder	100.00
2.00	6	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 and 2 with solution of items 3 and 4, pass through an 0.8-mm sieve, add items 5 and

6, and press with low-compression force. Compress 312 mg using 9-mm biconvex punches.

Glycerin Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Quantity/1000 Suppositories (g)
1800.00	1	Glycerin (glycerol)	1800.00
0178.00	2	Sodium stearate	178.00
0099.00	3	Purified water	99.00

MANUFACTURING DIRECTIONS

The suppository mass is manufactured at a temperature of 120°C. Care must be taken to see that molten suppository mass does not accidentally spill on the person. The inside of the vessel should not be touched with the bare hand as it is at a temperature of 120°C. Sodium stearate powder is light and fluffy; avoid inhaling the dust. Load item 1 into the mixer and heat to 120 ± 2°C while stirring at low

speed. Load item 2 into the mixer containing item 1. Mix until complete solubilization is achieved. Cool to 105 ± 2°C. Add item 3 slowly to the mixer containing the mass while stirring. Mix for 20 minutes. Immediately transfer the hot mass to the heated storage vessel or heated vessel of a Sarong SAAS suppository filling machine. Check the temperature; it should be 105 ± 2°C. *Fill weight:* 2077 mg per suppository.

Glycerin Suppositories for Children

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Quantity/1000 Suppositories (g)
900.00	1	Glycerin (glycerol) (0.06% excess)	900.50
089.00	2	Sodium stearate	89.00
049.50	3	Purified water	49.50

MANUFACTURING DIRECTIONS

Fill weight: 1039 mg per suppository. See directions under Glycerin suppositories.

Glycol Foam, Nonaqueous

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
40.00	1	Polawax A31	4.00
710.00	2	Propylene glycol	71.00
150.00	3	Ethanol DEB100	15.00

MANUFACTURING DIRECTIONS

Dissolve Polawax in propylene glycol/ethanol. Pack into containers and pressurize. Ethanol may be omitted if desired. In aerosol pack, 90% concentrate and 10% propellant 12/114

may be used. Propylene glycol is a suitable vehicle for glycol-soluble medicaments. The above formulation provides a mousse for such a system.

Guaifenesin Pseudoephedrine, Carbinoxamine, and Chlophedianol Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
20.00	1	Guaifenesin	20.00
400.00	2	Sucrose	400.00
240.00	3	Glucose liquid	240.00
120.00	4	Sorbitol solution	120.00
3.00	5	Saccharin sodium	3.00
2.50	6	Sodium benzoate (powder)	2.50
30.00	7	Pseudoephedrine hydrochloride	30.00
1.00	8	Carbinoxamine maleate	1.00
6.60	9	Chlophedianol hydrochloride	6.60
105.00	10	Dye Red E123 (Amaranth)	0.105
3.75	11	Dye Blue FD&C No. 1	3.75 mg
QS	12	Acid, hydrochloric	QS
50.00	13	Menthol crystals	50.00 mg
2.75	14	Flavors	2.75
65.00	15	Orange oil terpeneless	65.00 mg
5.66	16	Alcohol (190 proof)	5.664
GS	17	HyFlo filter aid	0.526
QS	18	Purified water	~420.00

MANUFACTURING DIRECTIONS

Charge 260 mL purified water into a suitable tank. Begin heating water to 70 to 80°C while adding guaifenesin and sucrose with stirring. Continue stirring to dissolve ingredients. Remove heat; add glucose liquid and sorbitol to solution from step above with stirring. Add saccharin sodium, sodium benzoate, pseudoephedrine hydrochloride, carbinoxamine maleate, and chlophedianol hydrochloride to solution from preceding step. Stir well to dissolve all ingredients. Dissolve Dye Red E123 and Dye Blue FD&C No. 1 in 10 mL warm purified water. Add dye solution to solution from

preceding step with stirring. Cool solution to 30 to 35°C. QS to 975 mL using purified water; mix well. Adjust to pH 4.25 (range 4 to 4.5) with hydrochloric acid (~0.65 g/L of drops). Stir well after each addition of acid. Dissolve menthol, flavors, and Orange Oil in alcohol; add mixture to solution from previous step with good stirring. Stir the solution slowly for 2 hours. Allow to stand overnight to cool and remove entrapped air. QS to 1 L with purified water; stir well. Add HyFlo filter aid to solution, and mix well. Recirculate through filter press or equivalent until sparkling clean.

Hemorrhoid Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
20.00	1	Lanolin alcohol (Ivarlan 3310)	20.00
448.00	2	Petrolatum	448.00
450.00	3	Petrolatum amber	450.00
30.00	4	Shark liver oil	30.00
10.00	5	Live yeast cell derivative (Biodyne's TRF)	10.00
10.00	6	Deionized water	10.00
20.90	7	Lanolin	20.90
1.00	8	Thyme oil	1.00
0.10	9	Phenyl mercuric nitrate	0.10

MANUFACTURING DIRECTIONS

Mix and heat items 1 to 4 to 70°C; cool to 50°C; and hold. Separately combine items 5 to 7 and heat to 40°C and mix until homogenous dispersion is achieved; with rapid mixing

add this mixture to previous mixture; mix again and cool to 40°C; add items 8 and 9. Continue mixing while cooling to 35°C.

Horsetail Extract Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
450.00	1	Horsetail extract (powder)	456.00
14.00	2	Kollidon® VA 64	14.00
5.00	3	Lutrol F 68	5.00
QS	4	Isopropanol	~120.00
14.00 g	5	Kollidon® CL	14.00
QS	6	Magnesium stearate	QS

MANUFACTURING DIRECTIONS

Granulate the extract (item 1) with solution of items 2 to 4; dry; pass through an 0.8-mm sieve; mix with items 5

and 6; and press with high compression force. Compress 489 mg using 12-mm biplanar punches.

Hydrocortisone Aqueous Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
10.00	1	Hydrocortisone acetate	10.00
100.00	2	Lutrol E 400	100.00
50.00	3	Cremophor RH 40	50.00
5.00	4	Carpopol 940 (Goodrich)	5.00
495.00	5	Water	495.00
QS	6	Preservative	QS
260.00	7	Water	260.00
8.00	8	Triethanolamine	8.00
—	10	Water	7.20

MANUFACTURING DIRECTIONS

Heat item 6 in item 7 to 80°C; prepare a solution of items 3 and 4 in item 5 and add to above solution of perservative.

Add and suspend item and mix. Prepare a solution of item 8 in item 10 and add to the above solution at 70°C and cool to form gel.

Hydrocortisone Aqueous Gel

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tabs. (g)
10.00	1	Hydrocortisone acetate	1.00/1.00
150.00	2	Cremophor A 25	—15.00
20.00	3	Cremophor RH 40	5.00/20.00
QS	4	Preservative	QS
640.00	5	Water	26.00/64.00

MANUFACTURING DIRECTIONS

Suspend item 1 in a mixture of items 2 and 3 at 70°C. Prepare solution of item 4 by heating item 5 to 70°C and

add it slowly to the hot item 4. Continue to stir until the gel is cool to form clear colorless gels.

Hydrocortisone Cream

Bill of Materials			
Scale (g /100 g)	Item	Material Name	Quantity/kg (g)
1.00	1	Hydrocortisone, micronized (3% excess)	10.30
6.00	2	Propylene glycol	60.00
0.10	3	Chlorocresol	1.00
5.00	4	Mineral oil (liquid paraffin)	50.00
2.00	5	Poloxyl 20 cetostearyl ether (Cetomacrogol 1000)	20.00
8.00	6	Cetostearyl alcohol	80.00
18.00	7	Petrolatum (white soft paraffin)	180.00
0.29	8	Monobasic sodium phosphate	2.90
0.035	9	Propyl paraben	0.35
0.10	10	Methyl paraben	1.00
59.60	11	Purified water	596.00

MANUFACTURING DIRECTIONS

Load 10 g of item 5 and items 4, 6, and 7 in fat-melting vessel. Heat to 70 to 75°C while stirring. Cool down the temperature to 65°C. Maintain temperature at 65 to 70°C. Heat item 11 to 90°C in mixer. Dissolve items 9 and 10 to a clear solution by stirring. Cool down the temperature to 65°C. Maintain temperature to 65 to 70°C. Add 10 g of item 5 and items 3 and 8 to the parabens solution to dissolve. Mix for 15 minutes. Maintain temperature at 65 to 70°C. Transfer oil phase to the aqueous phase in mixer vessel through mesh under vacuum while stirring at

manual mode (10 rpm) at a temperature of 60°C. Homogenize at high speed. Maintain temperature of 60°C. Vacuum at 0.4 bar for 10 minutes. Cool temperature to 45°C. Mix item 1 in 48.0 g of item 2 in a separate container at 45°C using homogenizer to make slurry. Add to the dispersed phase while mixing at 10 rpm and keep temperature at 45°C. Rinse the container with 12.0 g of item 2 and add to the dispersed phase. Mix and homogenize under vacuum at 0.4 bar for 10 minutes, low speed (10 rpm) at a temperature of 45°C. Cool the temperature to 30°C while mixing at 10 rpm in auto mode under a vacuum of 0.4 bar.

Hydrocortisone Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
70.00	1	Cetylstearyl alcohol	70.00
15.00	2	Cremophor A 6	15.00
15.00	3	Cremophor A 25	15.00
120.00	4	Liquid paraffin	120.00
2.00	5	Parabene	2.00
688.00	6	Water	688.00
80.00	7	Propylene glycol	80.00
10.00	8	Hydrocortisone	10.00

MANUFACTURING DIRECTIONS

Heat the mixture of items 1 to 5 and the water separately to about 80°C. Add the water to the obtained solution of items 1 to 5 with rigorous stirring. Heat items 7 to 8 until

the active ingredient is dissolved, mix with above and continue to stir while cooling to room temperature to produce a white cream.

Hydrocortisone Ethanolic Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
5.00	1	Hydrocortisone acetate	5.00
60.00	2	Cremophor RH 40	60.00
9.00	3	Triethanolamine	9.00
76.00	4	Water	76.00
600.00	5	Ethanol, 96%	600.00
5.00	6	Carbopol® 940 (Goodrich)	5.00
245.00	7	Water	245.00

MANUFACTURING DIRECTIONS

Prepare solution of items 6 and 7 and mix slowly with solution of items 1 to 5 to produce a clear, colorless gel.

Hydrocortisone Ointment

Bill of Materials			
Scale g /100 g	Item	Material Name	Quantity/kg (g)
1.00	1	Hydrocortisone, micronized (6% excess)	10.60
91.50	2	Petrolatum (white soft paraffin)	915.00
7.00	3	Mineral oil (liquid paraffin)	70.00
0.50	4	Sorbitain sesquioleate (Arlacel 83)	5.00

MANUFACTURING DIRECTIONS

Melt items 2 and 4 at 75°C in fat-melting vessel. Start heating mixer vessel to 75°C. Transfer molten items from first step to mixer through stainless steel mesh under vacuum at 0.4 to 0.6 bar. Start mixer at 10 rpm in manual mode. Cool down to 50°C. Disperse item 1 in 60.0 g of item 3 using a spatula in a water bath at 60°C. Homogenize for 6 minutes using homogenizer. Add this to mixer while

mixing. Rinse the homogenizer and container with 10.0 g of item 3, and transfer the rinsings to the mixer. Homogenize the dispersion under vacuum at 0.4 to 0.6 bar while stirring at 10 rpm in homogenizer at high speed for 10 minutes. Cool the temperature to 30°C, using a mixer speed 10 rpm and vacuum of 0.4 to 0.6 bar in auto mode. Transfer the ointment to stainless steel container.

Ibuprofen Pediatric Suspension

Bill of Materials			
Scale (mg/5mL)	Item	Material Name	Quantity/L (g)
100.00	1	Ibuprofen, low-density ^a	20.00
3000.00	2	Sucrose	600.00
10.00	3	Sodium benzoate	2.00
5.00	4	Saccharin sodium	1.00
5.00	5	Edetate disodium (sodium EDTA)	1.00
500.00	6	Glycerin (glycerol)	100.00
500.00	7	Sorbitol (70% solution)	100.00
10.00	8	Xanthan gum (Keltrol-F)	2.00
20.00	9	Microcrystalline cellulose (Avicel™ RC591)	4.00
5.00	10	Polysorbate 80 (Tween 80)	1.00
8.50	11	Citric acid	1.70
1.35	12	FD&C Red No. 40	0.27
7.50	13	Mixed fruits flavor	1.50
5.00	14	Strawberry flavor	1.00
QS	15	Purified water	QS to 1 L

^a Meets USP criteria with the following additional requirements: 100% particle size below 50 μm and tapped density of 0.3 to 0.4 g/mL.

MANUFACTURING DIRECTIONS

Heat 302.0 g of item 15 to 90°C and dissolve item 2 while mixing in mixer. Cool to about 50°C. Add items 3, 5, 4, 11, and 7 to mixer while mixing and dissolve. Filter the syrup through Seitz Supra 2600 filters in clean stainless steel tank. In a clean stainless steel vessel, dissolve item 10 in 35.0 g of item 15 (40°C). Add item 1 slowly while mixing with stirrer. Mix for 30 minutes to make uniform dispersion. *Caution:* Avoid excessive foaming. Disperse items 8 and 9 in item 6 in a clean and dry stainless steel container using stirrer. Add 75.0 g of hot item 15 (70 to 90°C) at once while mixing. Mix for 20 minutes to make a homogeneous smooth mucilage. Add about 500 g syrup, ibuprofen dispersion, and mucilage to the mixer. Rinse the containers of ibuprofen dispersion and mucilage with 50.0 g of item 15 (40°C). Add the rinsings to the mixer.

Set the mixer: temperature, 25°C, speed, 18 rpm; and manual mode vacuum at 0.5 bar. Mix for 3 minutes at low homogenizer speed. Mix for 2 minutes at homogenizer high speed. Check the suspension for uniformity of dispersion. Homogenize for additional 3 minutes at high speed, if required. Add the balance of the syrup (about 507.6 g) from previous step to the mixer. In a separate container, dissolve item 12 in 6.0 g of cooled item 15 (40°C) and transfer to the mixer. Add items 13 and 14 to the mixer. Set the mixer: temperature, 25°C; speed, 18 rpm; manual mode vacuum at 0.5 bar. Mix for 15 minutes. Mix for 5 minutes at homogenizer low speed. Mix for 5 minutes at homogenizer high speed. Check the suspension for uniformity. Adjust the final volume to 1 L by using purified water.

Ibuprofen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Ibuprofen	200.00
88.00	2	Maize starch	88.00
30.00	3	Maize starch	30.00
12.80	4	Maize starch (dried) ^a	12.80
1.60	5	Stearic acid (fine powder)	1.60
—	6	Purified water	144.00

^a Loss on drying: NMT 4.5% when dried at 120°C for 4 hours.

MANUFACTURING DIRECTIONS

Pass item 3 through a 250- μ m sieve using a sifter. Prepare a slurry of item 3 with 10.67 g of cold item 6 (25 to 30°C) in a stainless steel container. Pour the slurry into a vessel containing 37.33 g of hot item 6 (70 to 90°C). Heat to 80 to 90°C and mix until mixture swells and becomes translucent. Cool to 50°C. Check weight (theoretical weight, 58.00 g). If required, adjust with hot purified water. Record the quantity of extra water added. Pass items 1 and 2 through sifter using 250- μ m sieve. Load it into a mixer (if required, grind item 1 through a 1-mm sieve). Mix the powder for 15 minutes at high speed. Add binding solution to the dry powder in the mixer and mix for 15 minutes at high speed. Check for satisfactory wet mass. Pass the wet mass through a Fitz mill using sieve 24207, knives forward, medium speed. Collect and spread the granules onto the trays, one third the thickness of the tray.

Load the trolleys into the oven and dry the granules at 55°C for 36 hours. After 12 hours of drying, stir the granules in the trays and change the position of the trays for uniform drying. Check the moisture of the dried granules. The limit NMT is 2.5%. Dry further if required to obtain moisture content of 2.5%. Check the weight of dried granules (theoretical weight= 318.00 g). Pass the dried granules through a 1.5-mm sieve using a granulator. Collect in a stainless steel drum and add it to the blender. Pass items 4 and 5 through a 250- μ m sieve using a sifter. Add the sieved material to the granules in a blender and mix for 5 minutes. Compress 330 mg in 10-mm convex punches at 4 to 9 Kp. Coat the tablets using one of the polyvinylpyrrolidone (PVP) coating solutions provided in the Appendix or use the sugar-coating formulation given below:

Coating Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
7.06	1	Sandrac varnish (WMR)	7.06
3.33	2	Povidone (PVP K-25)	3.33
1.86	3	Povidone (PVP K-25)	1.86
175.85	4	Sucrose	175.85
0.16	5	Titanium dioxide	0.16
1.20	6	Polishing emulsion*	1.20
1.33	7	Talc (fine powder)	1.33
—	8	Purified water	87.10

Coating Manufacturing Directions

Load the tablets into the pan. Start the tablets rolling with the exhaust on and air supply off. Pour the item 1 solution onto the rolling tablets and allow the tablets to roll, using hand agitation if required, permitting the solution to spread well over the tablet bed. Permit the tablets to roll until tack develops, at which point item 7 should be quickly sprinkled over the tablets. Allow to roll freely for 2 minutes at 45°C. Do not roll too long, as the seal may be worn from the tablet edges. After two minutes of rolling, jog the tablets every 1 minute over a period of 15

minutes with exhaust and drying air on at 45°C. Continue jogging for a further 15 minutes. Jog every 3 minutes with exhaust and drying air temperature on at 45°C. Dissolve 2.40 g of item 2 in 28.80 g of item 8. Apply a half quantity of it to the tablets over 5 minutes; allow to dry and apply the remainder over a 15-minute period. Heat 11.52 g of item 8 to boiling, dissolve 26.88 g of item 4, and cool down to 25°C. Check weight (theoretical weight, 38.40 g). If less, adjust weight to 38.40 g with purified water. Apply sugar coat over a 30-minute period. Dry the tablets in the coating pan at 30°C, jogging every 1 hour for 6

hours. Heat 72.0 g of item 8 in mixer to boiling. Dissolve 168.0 g of item 4 and then cool to 25°C. Filter the syrup through a 180-µm stainless steel sieve. Dissolve item 3 in 3.68 g of item 8. Disperse item 5 in about 10.67 g of sugar syrup from the previous step and homogenize. Mix these steps with sugar syrup. Check for evenness of the dispersion. Apply sugar coating. Dissolve 4.53 g of item 4 in

5.33 g of item 8. Apply gloss solution. Add item 6 without air to the tablet bed carefully to get a uniform distribution while rolling. After 5 minutes of distribution, turn on the cold air and roll further until a shine appears. Once the desired polish appears, stop rolling the pan. Dry the tablets in the pan at 30°C for 30 minutes. Final tablet weight should be 480 mg.

* Item 6 Formulation

Bill of Materials		
Item	Material Name	Quantity/kg (g)
1	Bee's wax, bleached (white bee's wax)	28.75
2	Polyethylene glycol (PEG-6000)	70.00
3	Carnauba wax	57.50
4	Talc (fine powder)	125.00
5	Ethanol, 95%	718.75

Melt items 1, 2, and 3 in a steam-heated vessel by gentle heating to 70°C or in a stainless steel container on a hot-plate heater. Add item 4 to the vessel or stainless steel container and stir manually. Add item 5 to the vessel or

stainless steel container and stir manually. Pass the mixture through a homogenizer. Store the polishing emulsion in a closed container at room temperature.

Inosin Tablets

Bill of Materials			
Scale (g/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	I. Inosin (Ribaxin, Russia)	200.00
51.00	2	Lactose monohydrate	51.00
6.00	3	Kollidon® 90 F	6.00
QS	4	Isopropanol	60.00 mL
10.00	5	Kollidon® CL	10.00
3.00	6	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 3 with the solvent mixture of items 4; dry; pass through an 0.8-mm sieve; add items

5 and 6; and press with low compression force. Compress 270 mg in 9-mm biconvex punches.

Insect Bite Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
180.00	1	Trilaneth-4 phosphate, glyceryl stearate, and PEG-2 stearate	180.00
20.00	2	Hydrogenated palm/kernel oil PEG-6 esters	20.00
80.00	3	Mineral oil	80.00
0.30	4	Sodium methylparaben	0.30
0.70	5	Sorbic acid	0.70
646.70	6	Deionized water	646.70
10.00	7	Benzocaine	10.00
10.00	8	Butamben	10.00
2.00	9	Menthol	2.00
0.30	10	Resorcinol	0.30
50.00	11	Ethoxydiglycol	50.00

MANUFACTURING DIRECTIONS

Dissolve items 7 to 10 in item 11. Mix and heat items 1 to 6 to 75°C. Allow to cool slowly with constant stirring.

At 35°C add this to previous mixture. Homogenize if necessary.

Iron (Polymer Coated Particle) Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Elemental iron; use ferrous sulfate polymer-coated particles (233 mg iron per g ferrous sulfate)	450.60
200.00	2	Cellulose microcrystalline	200.00
254.40	3	Lactose monohydrate	254.40
36.00	4	Sodium starch glycolate	36.00
9.00	5	Magnesium stearate	9.00

Note: Factor in potency of ferrous sulfate polymer-coated particles. Adjust with item 3. Item 1 is prepared by first granulating ferrous sulfate using alcohol and water, drying, and sieving particles over 1200 µm in size. Regranulate smaller particles. Apply enteric (HPMC) coating to the granules in a fluid-bed dryer.

MANUFACTURING DIRECTIONS

Charge a suitable mixer/blender with microcrystalline cellulose and disperse the ferrous sulfate polymer-coated powder. To this mix, add about half the lactose (item 3) and blend for 5 minutes. Pass the sodium starch glycolate through a 500-µm sieve, followed by about half of the remaining lactose. Add to the mix. Blend for a further 5

minutes. Pass the magnesium stearate (item 5) through a 500-µm sieve, followed by the remaining lactose. Add to the previous mix. Blend for a further 5 minutes. Compress 950 mg per tablet at 8 to 14 kpi using 8 × 16-mm punches; do not rework tablets. Coat the tablets using a HPMC coating solution (see Appendix).

Iron Infant Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
0.18	1	Propyl paraben	0.18
0.022	2	Methyl paraben	0.02
1000.00	3	Sorbitol solution	1.00 kg
4.00	4	Citric acid (hydrous powder)	4.00
125.00	5	Iron sulfate	125.00
0.106	6	Sodium metabisulfite	0.10
0.50	7	Guarana flavor (artificial)	0.50
20.00	8	Alcohol (ethanol)	900.14
0.14	9	Dye	0.14
QS	9	Sodium hydroxide	QS
QS	10	Citric acid (powder)	1 QS
QS	11	Purified water	QS to 1 L
QS	12	HyFlo filter aid	1.00
QS	13	Liquid nitrogen	QS
QS	14	Carbon dioxide gas	QS

MANUFACTURING DIRECTIONS

The product is susceptible to oxidation. No effort should be spared to protect it from atmospheric air. Maintain carbon dioxide (CO₂) or nitrogen atmosphere where indicated. The product must be manufactured and held in a glass-lined or stainless steel tank. Product waiting to be filled should either be in a closed tank with a CO₂ atmosphere or in an open tank covered with polyethylene sheeting taped tightly with a constant slow stream of CO₂ gas flowing into the tank headspace. Avoid vortex formation throughout processing. Charge 144 mL of purified water into a mixing tank. Heat to 95 to 100°C and add parabens with strong agitation. Add sorbitol solution and citric acid (item 4) while mixing. Bring solution to 90°C while mixing. Cool the solution while mixing to 60 to 65°C, and hold at this temperature with CO₂ or

nitrogen gas bubbling into it. CO₂ gas protection is continued for the remainder of the manufacturing process. Add ferrous sulfate and dissolve while mixing, holding at 60 to 65°C. Cool to 25°C with mixing. Add sodium metabisulfite and dissolve while mixing. Avoid vortex formation. Dissolve dye in 2 mL of freshly boiled purified water and add to the tank. Mix. Dissolve the guarana flavor in alcohol, add to the tank, and mix. Check pH (range, 1.8 to 2.2). Adjust if necessary, with a solution of 10% sodium hydroxide or a solution of 10% citric acid. Make up to volume with freshly boiled purified water and mix. Readjust to volume if necessary with freshly boiled purified water, and mix. Add HyFlo filter aid and mix. Filter through press until clear. Bubble CO₂ or nitrogen gas into the clear filtrate for 5 minutes, then seal tank and hold product under CO₂ or nitrogen protection.

Iron Polystyrene and Vitamin C Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
125.00	1	Glycerin	125.00
1.40	2	Methyl paraben	1.40
0.16	3	Propyl paraben	0.16
79.61	4	Sorbitol; use sorbitol solution	364.33
3.30	5	Xanthan gum	3.30
10.00	6	Sucrose (granulated)	100.00
0.20	7	Saccharin (insoluble)	2.00
105.00	8	Elemental iron; use iron polystyrene sulfonate	530.31
50.00	9	Ascorbic acid, USP (35% excess)	61.95
0.10	10	Flavor	1.00 mL
0.10	11	Flavor (artificial guarana)	1.00 mL
QS	12	Sodium hydroxide	12. 1.0
QS	13	Dye	2.00
9.50	14	Distilled purified water	~95.00 mL
10.00	15	Sorbitol solution	~10.00

MANUFACTURING DIRECTIONS

Add glycerin (item 1) to the tank. Commence heating with agitation. Add and disperse parabens. Continue heating to 70 to 80°C and mix until solution is complete. Force cool to 30°C, then add and disperse xanthan gum (item 5). Add sorbitol solution (item 4) and 80 mL of purified water (item 14), and heat with mixing to 60 to 70°C until the xanthan gum is fully dissolved. Add and disperse saccharin and sugar (items 7 and 6). Mix at 60 to 70°C until dispersion is complete. Force cool to 25 to 30°C with continuous mixing. Commence N₂ gas protection and maintain for the remainder of the manufacturing process. Add and disperse ascorbic acid. Continue mixing for 30 mins at 25 to 30°C. (*Note:* Use suitable SS high-powered stirrer). Mix the iron polystyrene sulfonate milled slurry in the original epoxy-lined drums under N₂ gas protection until uniform. Add the slurry to the main batch and mix for 30 minutes at 25 to 30°C. (*Note:* Avoid scraping the

epoxy lining of the steel drum while mixing and use a plastic or rubber scraper to assist in complete transfer of the mixed slurry.) Add and disperse the flavors. Mix well. Check and record pH. Adjust pH using a 20% sodium hydroxide solution (1 g in 5 mL water) to a value of 3 (range, 2.8 to 3.2). Dissolve the dye in 5 to 7 mL of water at 40 to 45°C by stirring for 10 minutes. Add this solution to the main batch through a 420-μm screen with mixing. Rinse container with 2 to 3 mL water at 40 to 45°C and add to bulk through a 420-μm screen. Continue to mix under vacuum until mixture is uniform. Pass the suspension through the colloid mill at a gap setting of 100 to 150 μm. Adjust the flow rate such that the temperature rise of the suspension does not exceed 10°C. Collect the milled suspension in a stainless-steel-jacketed tank with vacuum. Mix at 25 to 30°C under vacuum until a uniform suspension is achieved. Flush the bulk suspension with nitrogen and seal. Hold at 25 to 30°C.

Kaolin–Pectin Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Quantity/L (g)
147.60	1	Sodium methyl paraben	4.92
6.72	2	Sodium propyl paraben	224.00
36.00	3	Magnesium aluminum silicate type IA	1.20
5832.00	4	Kaolin (powder)	194.40
130.00	5	Pectin	4.33
120.00	6	Sodium CMC (premium, low-viscosity)	4.00
210.00	7	Cyclamate calcium	7.00
21.00	8	Saccharin calcium (powder)	0.70
15.375	9	Flavor	0.51
1.234	10	Flavor	41.13
QS	11	Distilled purified water (approx.)	QS
QS	12	Citric acid (anhydrous powder)	QS

MANUFACTURING DIRECTIONS

Charge 600 mL of water into a suitable jacketed mixing tank. Add the methylparaben and propyl paraben to the tank and heat to 90 to 95°C. Cool to 70°C, add the magnesium aluminum silicate, and mix for 30 minutes or until evenly dispersed. Hold temperature at 70°C. Add kaolin with constant mixing at 70°C until evenly dispersed. Add pectin, and mix for 2 hours, maintaining a temperature of 70°C. Add the premium, low-viscosity sodium CMC, and mix for at least 30 minutes, maintaining a temperature of

70°C. Cool to 60°C, and hold at this temperature. Add, in order, the cyclamate calcium and saccharin calcium and mix thoroughly for 20 minutes. While mixing, cool to room temperature and allow to stand overnight to hydrate. After overnight standing (minimum 12 hours), mix for 30 minutes. Add flavors while mixing. Check and record pH (range, 4.5 to 7.5). If pH is above 7.5, adjust with a 60% solution of citric acid to the desired pH. Add water to 1 L and mix thoroughly for 3 hours. Strain product through muslin cloth into holding tanks and cover.

Kaolin–Pectin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
QS	1	Distilled purified water	300 mL
50.00	2	Corn starch	50.00
50.00	3	Povidone (K-29–32)	50.00
QS	4	Distilled purified water	0.50 L
630.00	5	Hydrated aluminum–magnesium silicate	630.00
100.00	6	Kaolin (powder)	100.00
50.00	7	Pectin	50.00
80.00	8	Corn starch	80.00
80.00	9	Sodium lauryl sulfate	7.00
10.00	10	Magnesium stearate	10.00

MANUFACTURING DIRECTIONS

Heat purified water (item 1) to 75 to 80°C, and add corn starch (item 2) with continuous stirring until a translucent paste is formed; use this paste within 1 hour. Dissolve Povidone in purified water (item 4) in a separate container. Ensure that dissolution is complete. Charge the following into a suitable planetary mixer: hydrated aluminum–magnesium silicate, kaolin, and pectin. Mix for 5 minutes. Add freshly prepared starch paste from the first step and the Povidone solution to the powder blend from the third step; mix until a mass of suitable consistency is obtained. Add extra purified water, if needed. Spread the wet mass on paper-lined trays and dry in the oven at 50°C for 2 hours. Pass the semidried mass through a 4.8-mm (4-mesh) screen by hand or by using a suitable granulator, and load the

granule mass onto paper-lined trays. Dry in the oven at 50°C until the moisture content is between 10.0 and 15.0%. Pass the dried granules through a 1.0-mm (18-mesh) screen on a comminuting mill at medium speed, knives forward, into clean, tared, polyethylene-lined drums; seal and weigh. Transfer the dried granules to a suitable blender. Screen the following items through a 595-μm (30-mesh) screen, and add to the blender: corn starch (item 8), sodium lauryl sulfate, and magnesium stearate. Blend for 5 to 10 minutes. Compress on a suitable compression machine using 1/2-inch round standard concave punches, upper punch with logo, and lower punch with a bisect line. Compress 977 mg at 10 to 18 kpi. Coat using an aqueous methocel coating and polish as desired.

Keratolytic Cream

Bill of Materials			
Scale (mg/10 g)	Item	Material Name	Quantity/kg (g)
150.00	1	Polawax (self-emulsifying wax)	15.00
150.00	2	PPG-2 myristyl ether propionate (CRODAMOL PMP)	15.00
50.00	3	Sorbital isostearate	5.00
35.00	4	Safflower oil, super-refined	3.50
20.00	5	Avocado oil, super-refined	2.00
20.00	6	Cetyl palmitate	2.00
50.00	7	Salicylic acid	5.00
1.50	8	Propylparaben	0.15
1.00	9	Butylated hydroxyl anisole	0.10
487.50	10	Deionized water	48.75
10.00	11	Sodium borate	1.00
3.00	12	Methylparaben	0.30
2.00	13	Imidazolidinyl urea	0.20
20.00	14	Hydrolyzed collagen + hyaluronic acid (CROMOIST HTA)	2.00

MANUFACTURING DIRECTIONS

Dissolve item 7 in item 2 with mixing and heating to 70°C; add balance of items 1 to 9 and mix with heat to 80°C. Mix items 10 to 13 together separately and heat to 80°C.

Add this mixture to the first mixture with mixing and cool to 40°C. Add item 14 with mixing and cool to the desired fill temperature. Adjust pH if necessary to 3.0 to 4.0 with 10% triethanolamine solution.

Khellin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Khellin	25
124.0	2	Ludipress®	124
1.00	3	Magnesium stearate	1

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix intensively, and press. Compress 150 mg in 8-mm biplanar punches.

Lidocaine Gel

Bill of Materials			
Scale (mg/10 g)	Item	Material Name	Quantity/kg (g)
20.00	1	Lidocaine hydrochloride	2.00
560.00	2	Water	56.00
200.00	3	Propylene glycol (Pharma)	20.00
220.00	4	Lutrol F 127	22.00

MANUFACTURING DIRECTIONS

Prepare solution of items 1 to 3 at room temperature, heat to 70°C or cool to 6°C, and slowly add item 4 to the well;

stir solution until it is dissolved. Maintain the temperature until the air bubbles escape to obtain a clear colorless gel.

Lidocaine Gel–Cream

Bill of Materials			
Scale (mg/10 g)	Item	Material Name	Quantity/kg (g)
50.00	1	Lidocaine hydrochloride	5.00
500.00	2	Water	50.00
150.00	3	Propylene glycol (Pharma)	15.00
100.00	4	Liquid paraffin	10.00
200.00	5	Lutrol F 127	20.00

MANUFACTURING DIRECTIONS

Prepare solution of items 1 to 3 at room temperature and mix with item 4. Heat to 70°C or cool to 6°C and slowly

add item 5 to the well; stir solution until it is dissolved. Maintain the temperature until the air bubbles escape.

Lidocaine Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Quantity/kg (g)
5.00	1	Lidocaine base	50.00
28.00	2	PEG-3350	280.00
40.00	3	PEG-400	400.00
25.00	4	Propylene glycol	250.00
2.00	5	Purified water	20.00

MANUFACTURING DIRECTIONS

Load items 2 and 3 into a fat-melting vessel. Heat to 70°C. Cool to 40°C while stirring at slow speed (10 to 12 rpm). Maintain the temperature between 40 and 45°C under continuous stirring. Heat 200.0 g of item 4 to 40 to 45°C in a stainless steel container. Dissolve item 1 by stirring with stirrer. Add item 5 under continuous stirring. Maintain the temperature between 40 and 45°C under continuous stirring. Filter through cloth filter. Transfer the drug solution into a mixer previously set with a temperature of 40 to 45°C. Rinse the stainless steel container with 50.0 g of item 4. Add the rinsing into the mixer. Transfer the

molten mass from the fat-melting vessel at 40°C through a stainless steel filter to the mixer containing the drug solution while mixing at 10 to 12 rpm. When the transfer is over, start the homogenizer at low speed, with a vacuum of 0.6 bar and stirrer speed of 10 rpm (manual mode). Mix and homogenize for 10 minutes with recirculation. Maintain temperature at 40 to 45°C. Stop the homogenizer, and set the mixer at temperature 25°C and stirrer speed at 10 rpm (manual mode). Cool the cream to 25°C. When the ointment is cooled to 25°C, unload the ointment into a stainless steel container.

Lidocaine, Eugenol, and Menthol Dental Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
55.20	1	Bee's wax (white, slabs)	55.20
150.00	2	Anhydrous lanolin (regular)	150.00
723.70	3	Petrolatum (white, regular)	723.70
40.00	4	Lidocaine base	40.00
1.20	5	Saccharin sodium (powder)	1.20
QS	6	Deionized, purified water	3.00 mL
1.00	7	Eugenol	1.00
5.00	8	Menthol (crystals)	5.00
0.80	9	Peppermint oil	0.80
20.16	10	Metaphen ointment base	20.16

MANUFACTURING DIRECTIONS

Melt bee's wax, lanolin, and petrolatum together at 70 to 80°C, and strain into a suitable container. Do not heat above 70 to 80°C. Mix together. Melt lidocaine base and strain into the container while mixing. Dissolve the sodium saccharin in purified water heated to 70°C. Add

to the container while mixing. Cool down to 45 to 50°C while mixing. Mix the eugenol, menthol, and peppermint oil together and liquefy. Warm gently to 35 to 40°C, if necessary. Strain into the container while mixing. Gently melt metaphen ointment base and strain into the container while mixing. Mix thoroughly until congealed.

Loratidine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Loratidine	10.00
67.30	2	Lactose monohydrate	67.30
22.00	3	Maize starch	22.00
10.00	4	Maize starch	10.00
5.00	5	Maize starch, dried	5.00
0.70	6	Magnesium stearate	0.70
QS	7	Purified water	QS

MANUFACTURING DIRECTIONS

Sift items 1 to 3 through a 630- μ m stainless steel sieve, load in mixer, and mix for 5 minutes. In a separate container, prepare binder solution by mixing item 4 using purified water at 30 to 40°C; heat translucent slurry to 90 to 95°C, and cool to 45 to 50°C. Mix the binder solution with the first step, and granulate; dry on trays at 55°C for

8 hours; dry to LOD of 2 to 3% (2 hours after beginning drying, crush mixture for uniform drying). Heat additional 1 hour at 55°C if LOD is not within limits. Add magnesium stearate; tumble mix, and compress using 7.00-mm round punches to 10 tablet weight of 1.15 (within 3%) to achieve thickness of 2.3 ± 0.3 mm and hardness of 4 to 7 kp.

Loratidine Fastab

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Loratidine (micronized)	10.00
180.60	2	Pharmaburst	180.60
2.70	3	Acesulfame K	2.70
2.00	4	Magnesium stearate	2.00
2.00	5	Talc (fine powder)	2.00
2.70	6	Dry anise flavor	2.70

MANUFACTURING DIRECTIONS

Sift and mix items 1, 2, 3, and 6. Lubricate with magnesium stearate and fine talc powder. Compress 200 mg in 6-mm punches.

Magaldrate Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Magaldrate, USP	500.00
400.00	2	Lactose monohydrate	400.00
50.00	3	Orange flavor (FDO)	50.00
20.00	4	Kollidon® 90 F	20.00
6.00	5	Banana flavor (FDO)	6.00
6.00	6	Cocoa flavor (FDO)	6.00
1.00	7	Saccharin sodium	1.00
180.00	8	Water	180.00
5.00	9	Aerosil® 200	5.00
3.00	10	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 3 with solution of items 4 to 8, pass through an 0.8-mm sieve, dry, mix with items 9 and 10, and press with low compression force. Compress 1 g in 16-mm biplanar punches.

Magaldrate Dispersible Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
700.00	1	Magaldrate	700.00
435.00	2	Lactose monohydrate	435.00
10.00	3	Kollidon® 90 F	10.00
50.00	4	Kollidon® CL	50.00
5.00	5	Magnesium stearate	5.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with low compression force (4 to 6 kN). Compress 1.2 g in 16-mm biplanar punches.

Magaldrate Instant Powder or Dry Syrup

Bill of Materials			
Scale (mg/Sachet)	Item	Material Name	Quantity/1000 Sachets (g)
800.00	1	Magaldrate, USP	800.00
640.00	2	Kollidon® CL-M	640.00
200.00	3	Sorbitol (crystalline)	200.00
40.00	4	Orange flavor	40.00
40.00	5	Kollidon® 90 F	40.00
4.00	6	Coconut flavor	4.00
4.00	7	Banana flavor	4.00
0.80	8	Saccharine sodium	0.80
QS	9	Water	~280.00 mL

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 4 with solution of items 5 to 9 and pass through an 0.8-mm sieve to obtain free-

flowing granules. Fill 2 g in sachets or 20 g in a 100-mL flask. *Instant granules in sachets:* Suspend 2 g (= one sachet) in a glass of water (= 800 mg magaldrate).

Magaldrate Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
100.00	1	Magaldrate USP	100.00
80.00	2	Kollidon® CL-M	80.00
20.00	3	Kollidon® 90 F	20.00
10.00	4	Orange flavor	10.00
0.50	5	Coconut flavor	0.50
0.80	6	Banana flavor	0.80
0.20	7	Saccharine sodium	0.20
QS	8	Preservatives	QS
QS	9	Water	QS to 1 L

MANUFACTURING DIRECTIONS

Dissolve or suspend all the solids in water under aseptic conditions; pH should be ~9.00.

Magaldrate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Magaldrate (powder, 100 mesh)	400.00
325.00	2	Sucrose	325.00
60.00	3	Cellulose (microcrystalline) (Avicel™ PH101)	60.00
30.00	4	Corn starch	30.00
8.84	5	Guar gum	8.84
0.50	6	Saccharin sodium	0.50
—	7	Purified water	100.00 mL
—	8	Alcohol SD 3A (200 proof)	100.00 mL
QS	9	Flavor	0.60 mL
QS	10	Flavor	1.00 mL
0.06	11	Ethyl vanillin	0.06
8.00	12	Talc	8.00
16.00	13	Magnesium stearate	16.0

MANUFACTURING DIRECTIONS

Pass granulated sugar (take about 10% excess) through 500- μ m stainless steel screen on comminuting mill (impact forward, high speed). Screen the milled sugar through 250- μ m aperture on sieve shaker. Weigh the required quantity and charge into a suitable mixer. Discard remaining sugar. Screen magaldrate powder (take about 5% excess) through 150- μ m stainless steel screen on sieve shaker. Weigh the required quantity and add to the blend above. Mix well. Screen, if necessary, microcrystalline cellulose, corn starch, and guar gum through 500- μ m aperture on sieve shaker. Add to the first step and mix well. Dissolve saccharin sodium in water. To this add alcohol and mix well. Add this hydroalcoholic solution to magaldrate blend and knead well. Add more water, if necessary, and QS to mass. Pass wet mass through 2.8-mm aperture on sieve shaker or oscillating granulator and spread uniformly on stainless steel trays. Tray-dry granules at 70 to 75°C. After 3 to 4 hours of drying, screen semidried granules through 1.4-mm aperture on sieve shaker, and reload for further drying. (This step helps in

drying granules faster and more uniformly.) Dry to LOD of 1 to 1.5%. Screen dried granules through 1.0-mm aperture on sieve shaker, and store in drums doubly lined with polyethylene bags. Charge half of the granulation into a suitable blender. From the balance of the granules, take out the fines (about 40 g of fines for a batch of 1000 tablets) through 250- μ m aperture on sieve shaker. Retain coarse particles for later use. Mix together the flavors in a suitable vessel. Add and dissolve the ethyl vanillin. Check that the solution is clear before proceeding. Charge a suitable mixer with the fines from above. While mixing, disperse the flavor solution. Add magnesium stearate and talc and mix thoroughly. Pass the blend through a 250- μ m aperture on sieve shaker. Add the dispersed flavor blend to the granules. Add remaining granules and blend for 8 to 10 minutes. Discharge blended granules into suitable air-tight containers doubly lined with polyethylene bags. Compress on a suitable machine fitted with 14.4-mm-diameter round punches with beveled edges. Weight: 8.5 g/10 tablets; thickness, ~3.6 to 3.8 mm; hardness: 8 to 10 kPa.

Magaldrate with Simethicone Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Quantity/L (g)
QS	1	Distilled purified water	285.00 mL
9.00	2	Methyl paraben	1.80
1.00	3	Propyl paraben	0.20
5.00	4	Benzoic acid	1.00
3.75	5	Saccharin sodium (dihydrate powder)	0.75
400.00	6	Magaldrate (wet cake; 18 to 20%)	400.00
1.00 g	7	Sorbitol solution (70%)	260.00
12.50	8	Silicon dioxide (colloidal) (International)	2.50
QS	9	Citric acid (hydrous powder)	QS
200.00	10	Dimethyl polysiloxane emulsion (30%)	40.00
0.005 mL	11	Flavor	1.00 mL
1.26 g	12	Glycerin	252.00
25.00 g	13	Potassium citrate monohydrate	5.00
13.30	14	Xanthan Gum	2.66

MANUFACTURING DIRECTIONS

This product is highly prone to microbial contamination. All equipment coming into contact with the product should be treated with a freshly prepared sodium hypochlorite solution (100 ppm), made with freshly boiled and cooled down water on the day of use. Bottles and caps should also be so treated. Freshly boiled and cooled deionized water should be used for rinsing. Charge 285 mL purified water into a suitable jacketed tank and heat to 90 to 95°C. Add and dissolve parabens, benzoic acid, saccharin sodium, and potassium citrate. While maintaining temperature at 85 to 90°C, add, in small quantities, half the quantity of magaldrate cake or powder, if used, and disperse well. (Adjust speed of the agitator and homogenizer to ensure effective mixing and to maintain free mobility of the suspension.) Add sorbitol solution and mix well. Raise the temperature, if necessary, main-

taining temperature at 85 to 90°C. Add in small quantities the remaining half of the magaldrate cake or powder, and disperse well. Mix for 1 hour and then remove heat. (Adjust speed of the agitator and homogenizer to maintain the mobility of suspension.) Separately blend colloidal silicon dioxide with xanthan gum and disperse the blend in glycerin, with constant mixing. While maintaining temperature at 85 to 95°C, add and disperse the suspension from the previous step to the main tank, and mix well. Avoid lump formation at any stage. Cool to room temperature. Add dimethyl polysiloxane emulsion and mix well. Add flavor and mix well. Dissolve citric acid in twice the quantity of purified water, and adjust pH if necessary. Check and record pH (range, 7.5 to 8). Add purified water to volume and mix well for a minimum of 30 minutes. Filter through a 180-µm aperture nylon cloth, and store in a suitable tank.

Magaldrate with Simethicone Tablet

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
525.00	1	Sucrose, NF	525.00
15.00	2	Lactose monohydrate, NF	15.00
60.00	3	Simethicone, USP	60.00
60.00	4	Cellulose microcrystalline (Avicel™ PH101), NF	60.00
12.00	5	Silicone dioxide colloidal (International)	12.00
400.00	6	Magaldrate, USP	400.00
40.00	7	Acacia (special grade), NF	40.00
0.05	8	Dye	0.05
—	9	Distilled purified water, USP	100.00 mL
—	10	Alcohol SD 3A (200 proof)	100.00 mL
1.50	11	Flavor	1.50
0.15	12	Ethyl vanillin, NF	0.15
5.00	13	Silicon dioxide (colloidal)	5.00
30.00	14	Starch monohydrate	30.00
10.00	15	Lactose monohydrate	10.00
80.00	16	Talc powder, USP	80.00
5.30	17	Magnesium stearate	5.30

MANUFACTURING DIRECTIONS

Pass the granulated sucrose (with about 10% excess) through a 500- μ m-aperture stainless steel screen on comminuting mill (impact forward, high speed). Screen the milled sugar through a 250- μ m screen on sieve shaker. Weigh the required quantity and charge into a suitable mixer (planetary mixer or dough mixer). Discard the remainder. Screen lactose (item 2) through a 250- μ m aperture screen on sieve shaker and add to powdered sugar from step above. Mix well. While mixing vigorously, add and disperse simethicone (add slowly in a fine stream of flow to avoid lump formation). Mix well. Rough blend colloidal silicon dioxide (item 5) and microcrystalline cellulose, and add to the simethicone dispersed mass from previous step. Mix initially at low speed for 4 to 5 minutes and thereafter mix vigorously for 5 to 10 minutes. Either screen simethicone dispersed mass through a 1.0-mm aperture on sieve shaker or pass through a comminuting mill using a 1.4-mm aperture screen (impact forward, medium speed). Load into a mass mixer and continue mixing. Screen magaldrate powder (with about 7% excess) through a 150- μ m aperture screen on sieve shaker, and weigh the required quantity. To this quantity add acacia and rough blend. Add this blend in the dough mixer, dispersing in small quantities, and mix well for 30 to 40 minutes until simethicone is well absorbed in the dry blend. Discard remaining magaldrate powder. Dissolve dye in water, then add alcohol and mix well. Wet down mass with colored hydroalcoholic solution, and knead well. Add more hydroalcoholic solution, if necessary (water:alcohol, 1:1), to mass. Screen wet mass through a

2.8-mm aperture screen on sieve shaker or oscillating granulator and spread uniformly on trays. Tray-dry granules at 71 to 74°C until LOD is within 1 to 1.5% (test at 105°C for 1 hour). After about 3 to 4 hours of drying, screen semidried granules through a 1.4-mm aperture on sieve shaker and reload for further drying. (*Note:* This step helps in drying granules faster and more uniformly and avoids color mottling on final product.) Screen dried granules through a 1.0-mm aperture screen on sieve shaker, and store in drums lined with double polyethylene bags. Alternative drying can be done in a fluid-bed dryer. Pass dried granules through a 1.00-mm aperture screen on sieve shaker. Pass coarse granules through a comminuting mill using a 1.4-mm aperture screen (knives forward, slow speed) and then through 1.0-mm aperture on sieve shaker. Store granules in drums lined with double polyethylene bags. Charge half of the base granulation into a suitable blender. From the balance of the granules take out fines (about 50 g of fines for a batch of 1000 tablets) through a 250- μ m aperture on sieve shaker, and hold in a suitable vessel. Add and dissolve ethyl vanillin in liquid flavor. Check for clarity, and only then disperse over dried starch. Rough blend colloidal silicon dioxide (item 13) with lactose monohydrate (item 15), talc, and magnesium stearate, and add to the flavored starch. To this mixture, add fines from the second step above, and mix well by hand or in a suitable mixer. Screen through a 250- μ m aperture on sieve shaker. Add this flavored, dispersed blend to the base granulation (first step) in a blender. Add the remaining bulk granules from the second step to the base granulation and blend well for 8 to 10 minutes. (*Caution:* Do not mix for too long as the granules may crumble to a finer size,

which may adversely affect hardness during compression.) Discharge blended granules into suitable airtight containers lined with double polyethylene bags until ready

for compressing. Compress on a suitable machine fitted with 14.4-mm-diameter round punches with beveled edges. Compress 1244 mg per tablet.

Magnesium Carbonate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
260.00	1	Magnesium carbonate, USP	262.00
238.00	2	Ludipress®	238.00
4.00	3	Magnesium stearate	4.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with medium compression force. Compress 500 mg in 12-mm biplanar punches.

Medicated Foot Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
5.00	1	Lanolin	5.00
90.00	2	Stearic acid	90.00
5.00	3	Cetyl alcohol	5.00
40.00	4	Isopropyl palmitate	40.00
10.00	5	Oleyl alcohol	10.00
20.00	6	Mineral oil and lanolin alcohol (Liquid Base CB3929)	20.00
7.50	7	Oil of wintergreen	7.50
3.00	8	Oil of thyme	3.00
5.00	9	Oil of pine	5.00
5.00	10	Menthol	5.00
5.00	11	Camphor	5.00
QS	12	Deionized water	QS to 1 kg
80.00	13	Glycerin	80.00
18.00	14	Triethanolamine 99%	18.00
QS	15	Preservative, color	QS

MANUFACTURING DIRECTIONS

Heat oil and water phases separately at 65 to 70°C. Add water phase to oil phase while stirring. Add the triethano-

lamine drop-wise. Stir to cool. This product can be used as a disinfecting and soothing cream for the feet.

Methyl Salicylate Heat Rub Lotion

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
25.00	1	PPG-5-Cetech-10-Phosphate (Crodafos SG)	25.00
40.00	2	Emulsifying wax, NF (Polawax)	40.00
45.00	3	PPG-1 cetyl ether (Procetyl 10)	45.00
10.00	4	Menthol	10.00
10.00	5	Camphor	10.00
75.00	6	Methyl salicylate	75.00
30.00	7	Glycerin	30.00
10.00	8	Gelatin, NF (Crodyne BY-19)	10.00
3.00	9	Diethanolamine	3.00
742.00	10	Deionized water	742.00
10.00	11	Propylene glycol, diazolidinyl urea, methyl paraben, and propyl paraben	10.00

MANUFACTURING DIRECTIONS

Premix items 4, 5, and 6 with item 3. When completely dissolved, add items 1 and 2 and heat to 75 to 80°C. Dissolve item 8 in water, and add items 7 and 9. Heat to

80°C; slowly add this part to previous part using good mechanical mixing. Allow to cool while mixing to 40°C, and then add item 11. Cool to 30°C, and fill.

Methyl Salicylate Analgesic Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
30.00	1	Tromethamine magnesium aluminum silicate (Veegum® PRO)	30.00
30.00	2	Hydroxypropylcellulose	30.00
350.00	3	Deionized water	350.00
350.00	4	Ethanol	350.00
40.00	5	Cocoyl sarcosine (Vanseal CS)	40.00
25.00	6	Oleath-10	25.00
25.00	7	PEG-25 hydrogenated castor oil	25.00
50.00	8	Isopropyl myristate	50.00
20.00	9	Triethanolamine	20.00
5.00	10	Camphor	5.00
5.00	11	Menthol	5.00
2.00	12	Eucalyptus oil	2.00
65.00	13	Methyl salicylate	65.00
QS	14	Preservatives	QS

MANUFACTURING DIRECTIONS

Dry blend item 1 and item 2, and slowly add them to items 2 and 4, agitating to ensure homogenous dispersion.

Combine items 5 to 9 separately and items 10 to 14 separately, then mix them together. Finally, add this mixture to the first mixture, and mix until uniform.

Methyl Salicylate Analgesic Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
15.00	1	Magnesium aluminum silicate (Veegum®)	1.50
547.00	2	Deionized water	54.70
2.00	3	Simethicone emulsion	0.20
30.00	4	Propylene glycol	3.00
150.00	5	Methyl salicylate	15.00
50.00	6	Menthol	5.00
6.00	7	Polysorbate	0.60
50.00	8	C18–C36 acid	5.00
150.00	9	Glycerl stearate and PEG-100 stearate	15.00
QS	10	Preservatives	QS

MANUFACTURING DIRECTIONS

Add item 1 to water slowly and mix vigorously to smooth dispersion. Add items 3 and 4, mixing one at a time; heat

to 75 to 80°C. Separately mix and heat items 5 to 9 to 75 to 80°C, and combine the two parts while mixing. Cool while mixing and add item 10 at 40°C.

Methyl Salicylate and Menthol Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
110.00	1	Methyl salicylate	110.00
50.00	2	Menthol	50.00
200.00	3	Lutrol E 400	200.00
60.00	4	Cremophor RH 40	60.00
70.00	5	Propylene glycol (Pharma)	70.00
320.00	6	Lutrol F 127	320.00
QS	7	Water	190.00

MANUFACTURING DIRECTIONS

Dissolve item 6 in solution of items 1 to 5, and mix with item 7. The clear gel can be diluted with water. Due to the high concentration of the active ingredients and of

Lutrol F 127, the consistency of the colorless clear gel is extremely hard. By reducing the concentration of the active ingredients, the amount of Lutrol F 127 can also be reduced, and the consistency of the gel will be normal.

Metoclopramide Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Anhydrous metoclopramide hydrochloride; use metoclopramide hydrochloride	10.54
7.00	2	Maize starch (dried)	7.00
1.00	3	Silicon dioxide (colloidal)	1.00
0.76	4	Magnesium stearate	0.76
5.00	5	Starch (pregelatinized)	5.00
101.24	6	Lactose	101.24
QS	7	Purified water	~15.00 mL

MANUFACTURING DIRECTIONS

Dried maize starch must be used for lubrication. Dry the starch at 80°C for 36 hours prior to its use in manufacturing. Check LOD of starch; the LOD must be less than 2.0%. Pass the lactose, pregelatinized starch, and metoclopramide hydrochloride through a 1.25-mm aperture screen, and transfer it to a suitable mass mixer; mix for 5 minutes. Add the water slowly to the mixer, and mix for 30 minutes or until a suitable consistency is obtained. Add extra water, if required. Pass the mass through a 4.80-mm aperture screen or an oscillating granulator (or by hand), and dry in a tray dryer or fluid-bed dryer at 50°C until the moisture content is below 5.5%. Pass the granules through

a 875-µm aperture screen on an oscillating granulator (or comminuting mill at medium speed, knives forward) into tared, polyethylene-lined drums; seal and weigh. Carry out remaining steps at a relative humidity below 50% and temperature below 26°C. Transfer the dried granulation to a suitable blender. Screen the starch (item 2), magnesium stearate, and silicon dioxide through a 250-µm aperture screen on a sieve shaker, and add to the blender. Blend for 10 minutes. Discharge the granules into polyethylene-lined drums; seal and weigh for yield. Compress 1.255 g per 10 tablets in 6.35- or 7.14-mm standard concave punches.

Miconazole Nitrate Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
21.00	1	Miconazole nitrate (5% excess)	21.00
200.0	2	Tefose 63	200.0
30.00	3	Labrafil M ^a	30.00
30.00	4	Mineral oil (liquid paraffin)	30.00
0.05	5	Butylated hydroxyanisole	0.05
2.00	6	Benzoic acid	2.00
720.00	7	Purified water	720.00

^a Synonyms: Labrafil M 1944 CS, oleoyl macroglycerides, apricot kernel oil PEG-6 complex.

MANUFACTURING DIRECTIONS

Melt items 3, 4, and 2 (fatty phase) in fat melting vessel. Heat to 65 to 70°C. Disperse items 5 and 1 in the fatty phase while mixing at high speed for 20 minutes. Add item 7 to the mixer, and heat to 80 to 90°C. Dissolve item 6, and cool down to 65 to 70°C. Transfer the fatty phase

to the mixer with vacuum at 0.2 to 0.3 bar. Start cooling down while mixing at 10 rpm, and homogenize at high speed for 20 minutes, then cool down to 25 to 28°C while mixing at a vacuum of 0.2 to 0.3 bar (65 to 45°C) or 0.5 to 0.7 bar (45 to 25°C).

Mineral and Multivitamin Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
6.65	1	Hypophosphorous acid	6.655
16.47	2	Calcium hypophosphite	16.47
31.68	3	Calcium lactate (powder)	31.68
1.00	4	Methyl paraben	1.00
0.20	5	Propyl paraben	0.20
1.00	6	Benzoic acid	1.00
150.00	7	Sucrose (granular)	150.0
5.20	8	Ferrous gluconate	5.20
2.00	9	Niacinamide (5% excess)	2.10
0.328	10	Riboflavin-5-phosphate sodium	0.33
1.00	11	D-pantothenyl alcohol (dexpantenol; 20% excess)	1.20
0.60 mcg	12	Vitamin B12 (cyanocobalamin) (35% excess)	0.81 mg
0.20	13	Pyridoxine hydrochloride	0.20
0.30	14	Thiamine hydrochloride (regular powder) (55% excess)	0.46
4.782	15	Flavor, raspberry blend	4.78
1.945	16	Flavor, chocolate	1.945
0.642	17	Orange oil (terpeneless, No. 54125)	0.64
0.21	18	Lime oil, distilled	0.215
4.28	19	Alcohol	4.28
2.50	20	Saccharin sodium	2.50
10.00	21	Ascorbic acid (white powder/EP) (45% excess)	14.50
3.00	22	Caramel (acid proof)	3.00
2.00	23	Anhydrous citric acid	2.00
10.0 mcg	24	Butylated hydroxyanisole (BHA)	10.0 mg
3.39	25	Corn oil	3.39
0.40	26	Vitamin A palmitate (1.5 MM U/g) (40% excess)	0.56
0.08	27	Viosterol in corn oil (<i>syn.</i> oleovitamin D; 1000 mg/g) (40% excess)	0.112
1.5 G	28	Acacia (special grade)	1.50
0.127	29	Sodium lauryl sulfate (acetone-washed)	0.127
171.00	30	Deionized, purified water	~171
QS	31	Glucose liquid (corn syrup)	QS to 1 L

MANUFACTURING DIRECTIONS

Do not expose this preparation during manufacturing to direct sunlight. Riboflavin is sensitive to light. Add 83.7 mL purified water to a stainless-steel-jacketed tank. Add calcium hypophosphite, calcium lactate, the parabens, and benzoic acid. Heat mixture to 60°C with agitation. Shut off mixer, and wash tank until free of all powders with 25.9 mL purified water. Heat to and maintain a maximum temperature of 100°C until solution is complete. Do not agitate. Avoid loss of water through evaporation; cover opening of tank. After solution occurs, take sample from bottom of tank and examine for clarity. Solution must be clear. Add hypophosphorous acid (if used) with mixing. Turn off heat, add 222.0 g glucose, and start agitator. (*Caution:* Use CO₂ cover throughout; wherever water is used, it should be CO₂-saturated water.) Dissolve ferrous gluconate in 7.4 mL water CO₂-saturated by heating. Add 278 g glucose with mixing. Add and dissolve sugar. Allow solution to cool to 35°C, and mix

well. To 29.6 mL water add and dissolve nicotinamide, riboflavin, D-pantothenyl alcohol, vitamin B12, pyridoxine, and thiamine. Mix until solution is complete, and add to tank. Dissolve by heat, if necessary. Charge raspberry blend flavor and chocolate flavor into tank; charge saccharin into tank, and mix until dissolved. Charge ascorbic acid into tank, mix well. Charge caramel into tank, and mix well. Dissolve citric acid in 3 mL water, and add. Heat corn oil to 50 to 60°C, and add and dissolve BHA. Be sure the BHA is completely dissolved before continuing. Cool to room temperature. While cooling oil mixture, saturate with CO₂ and maintain heavy CO₂ coverage for balance of operation. Set aside a small amount of this mixture as a rinse for the vitamin A and viosterol containers in step above. Add vitamin A palmitate and viosterol to the cool corn oil mixture, rinsing the containers with the oil reserved above. Add the rinse to the bulk. Mix well. Add the acacia to the oil mixture with good mixing. Dissolve sodium lauryl sulfate in 3 mL CO₂-saturated purified water. To avoid excessive foaming, do not

bubble CO₂ gas through the water/sodium lauryl sulfate solution. Add the sodium lauryl sulfate solution to the oil mixture, and stir to a thick creamy emulsion. Add 7.56 g glucose to the emulsion with mixing. Blend 13.33 mL CO₂-saturated purified water with 77.04 g glucose, and add emulsion with stirring. Recycle primary emulsion back into holding tank while setting mill. Homogenize until all oil globules are less than 8 µm in diameter using colloid mill with a very

fine setting. Do not change mill setting after removing sample unless samples are unacceptable. Add primary emulsion to syrup solution with mixing; add glucose QS to 965 mL, and mix well. Allow to stand overnight to vent entrapped air. Adjust the volume to 1 L using glucose or glucose and CO₂-saturated water. Strain through 149-µm aperture or similar screen into clean reserve tank, and recheck volume.

Mint-Menthol Mouthwash

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
20.00	1	Mint oil	20.00
0.40	2	Menthol	0.40
0.90	3	Eucalyptus oil	0.90
10.00	4	α-Bisabolol (BASF)	10.00
0.60	5	Thymian oil	0.60
40.00	6	Cremophor RH 40	40.00
4.50	7	Saccharin sodium	4.50
2.00	8	Sodium citrate	2.00
5.00	9	Citric acid	5.00
0.20	10	Sodium fluoride	0.20
50.00	11	Glycerol	50.00
50.00	12	Lutrol F 127	50.00
0.60	13	Salicylic acid	0.60
1.00	14	Benzoic acid	1.00
175.00	15	Sorbitol, crystalline	175.00
216.00	16	Ethanol 96%	216.00
QS	17	Sicovit colorant	QS
QS	18	Water	48.40

MANUFACTURING DIRECTIONS

Mix items 1 to 6, and heat to about 60°C. Prepare solution of items 7 to 18, heat it to about 60°C, and add it slowly

to the well-stirred mixture of items 1 to 6. Clear, colored liquids have a fresh mint taste.

Menthol Mouthwash

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
10.00	1	Menthol	10.00
10.00	2	Eucalyptus oil	10.00
40.00	3	Cremophor RH 40	40.00
4.50	4	Saccharin sodium	4.50
2.00	5	Sodium citrate	2.00
5.00	6	Citric acid	5.00
50.00	7	Lutrol F 127	50.00
67.00	8	Ethanol 96%	67.00
QS	9	Sicovit colorant	QS
QS	10	Water	801.00

MANUFACTURING DIRECTIONS

Mix items 1 to 3, and heat to about 60°C. Prepare solution of items 4 to 10, heat it to about 60°C, and add it slowly to the well-stirred mixture of items 1 to 3. Clear, colored liquid has a fresh mint taste.

Mint Oil Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
35.00	1	Peppermint oil	35.00
138.00	2	Cremophor RH 40	138.00
520.00	3	Ethanol 96%	520.00
QS	4	Water	307.00

MANUFACTURING DIRECTIONS

Mix the peppermint oil with Cremophor RH 40, stir well, and slowly add ethanol and water. Clear, colorless liquid is of low viscosity.

Multivitaminm, Calcium, and Iron Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Vitamin A acetate (dry powder)	5.00
2.00	2	Vitamin D (dry powder; 500,000 IU/g) (BASF)	2.00
1.20	3	Thiamine mononitrate (100,000 IU/g) (BASF)	1.20
1.80	4	Riboflavin, BASF	1.80
12.00	5	Nicotinamide	12.00
4.00	6	Vitamin E acetate (dry powder; SD 50)	4.00
50.00	7	Ascorbic acid (powder), BASF	50.00
60.00	8	Ferrous fumarate	60.00
200.00	9	Dibasic calcium phosphate granulated with 5% Kollidon® 30	200.00
125.00	10	Calcium carbonate	125.00
45.00	11	Avicel™ PH101	45.00
1.50	12	Aerosil® 200	1.50

MANUFACTURING DIRECTIONS

Mix all components, pass through a sieve, and press to tablets. Compress 500 mg in 11-mm biplanar punches.

Multivitamin and Calcium Syrup

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/100 g (mg)
0.10	1	Vitamin A palmitate	10.00
0.50 mcg	2	Vitamin D 40 mio IU/g	0.05
1.00	3	Vitamin E acetate, BASF	100.00
0.02	4	Butylhydroxytoluene	2.00
45.00	5	Cremophor RH 40	4.50 g
100.00	6	Water	10.00 g
450.00	7	Saccharose	45.00 g
2.00	8	Methyl parabene	200.00
0.80	9	Citric acid	80.00
96.00	10	Glycerol	9.60 g
0.70	11	Calcium gluconate	70.00
250.00	12	Water	25.00 g
0.15	13	Thiamine hydrochloride, BASF	15.00
0.15	14	Riboflavin 5'-phosphate sodium	15.00
0.55	15	Nicotinamide	55.00
0.15	16	Pyridoxine hydrochloride (BASF)	15.00
3.00	17	Ascorbic acid, crystalline (BASF)	300.00
1.00	18	Sorbic acid	100.00
50.00	19	Propylene glycol (Pharma)	5.00 g

MANUFACTURING DIRECTIONS

Heat items 1 to 5 and item 6 separately to about 60°C, and mix slowly, stirring well to obtain a clear solution. Dissolve items 7 to 9 in the hot solution of items 10 to

12 to obtain a clear solution. Mix all the solutions upon cooling, and add solutions of items 13 to 19; adjust the pH value to 4.0 to 4.1. Pass during 10 min nitrogen through the solution and fill in bottles under nitrogen cover.

Multivitamin and Carbonyl Iron Tablets

Bill of Materials			
Scale (per tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5000 IU	1	Vitamin A acetate (dry powder; 500,000 IU/g) (BASF)	10.00
2.20 mg	2	Thiamine mononitrate, BASF	2.20
2.20 mg	3	Riboflavin (BASF)	2.20
16.50 mg	4	Nicotinamide	16.50
11.50 mg	5	Calcium D-pantothenate (BASF)	11.50
2.20 mg	6	Pyridoxine hydrochloride (BASF)	2.20
6.00 mg	7	Cyanocobalamin (dry powder; 0.1%)	6.00
85.00 mg	8	Ascorbic acid (powder) (BASF)	85.00
31.00 mg	9	Vitamin E acetate (dry powder; SD 50)	31.00
311.00 mg	10	Ludipress®	311.00
10.00 mg	11	Carbonyl iron (powder OF) (BASF)	10.00
3.00 mg	12	Magnesium stearate	3.00
7.20 mg	13	Orange flavor	7.20
2.50 mg	14	Saccharin sodium	2.50

MANUFACTURING DIRECTIONS

Mix all ingredients, pass through an 0.8-mm sieve, mix, and press with high compression force (20 kN). Compress 500 mg in 12-mm biplanar punches.

Multivitamin and Mineral Tablets with Beta Carotene

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
150.00	1	Beta carotene (dry powder; 10%)	150.00
2.50	2	Thiamine mononitrate (BASF)	2.50
2.90	3	Riboflavin (BASF)	2.90
2.00	4	Pyridoxine hydrochloride (BASF)	2.00
22.00	5	Nicotinamide	22.00
12.00	6	Calcium D-pantothenate (BASF)	12.00
110.00	7	Ascorbic acid for direct compression	110.00
550.00	8	Calcium phosphate (dibasic)	550.00
82.00	9	Ferrous fumarate	82.00
166.00	10	Magnesium oxide	166.00
2.50	11	Cupric sulfate	2.50
13.80	12	Manganese sulfate	13.80
57.20	13	Potassium chloride	57.20
37.00	14	Zinc sulfate	37.00
57.00	15	Avicel™ PH102	57.00
50.00	16	Kollidon® CL	50.00
5.70	17	Stearic acid	5.70
5.00	18	Magnesium stearate	5.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with high compression force. Compress 1300 mg per tablet using 16-mm biplanar punches.

Multivitamin and Mineral Syrup

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/L (g)
6.65	1	Hypophosphorous acid (50% pure)	6.655
16.47	2	Calcium hypophosphite	16.47
31.68	3	Calcium lactate (powder)	31.68
1.00	4	Methyl paraben	1.00
0.20	5	Propyl paraben	200.00 mg
1.00	6	Acid benzoic	1.00
150.00	7	Sucrose	150.00
5.20	8	Ferrous gluconate	5.20
2.00	9	Niacinamide (white powder) (5% excess)	2.10
0.32	10	Riboflavin-5-phosphate sodium	328.77 mg
1.00	11	D-Pantothenyl alcohol (dexpantenol; 20% excess)	1.20
0.00060	12	Vitamin B12 (cyanocobalamin; 35% excess)	810.00 mcg
0.20	13	Pyridoxine hydrochloride	200.00 mg
0.30	14	Thiamine hydrochloride (powder, regular) (55% excess)	465.00 mg
4.78	15	Flavor, raspberry blend	4.782
1.94	16	Flavor, chocolate	1.945
0.64	17	Orange oil, terpeneless No. 54125	642.00 mg
0.21	18	Lime oil (distilled)	214.975 mg
4.28	19	Alcohol (ethanol, 190 proof)	4.28
2.50	20	Saccharin sodium	2.50
10.00	21	Acid ascorbic (45% excess)	14.50
3.00	22	Caramel (acid proof)	3.00
2.00	23	Anhydrous citric acid	2.00
0.0010	24	Butylated hydroxyanisole (BHA)	10.0 mg
3.39	25	Corn oil	3.39
0.56	26	Vitamin A palmitate (1.5 MM UA/g) (40% excess)	560.00 mg
0.08	27	Viosterol in corn oil (<i>syn.</i> oleovitamin D; 1000 mD/g; D3 in arachis oil) (40% excess)	112.00 mg
1.50	28	Acacia	1.50
0.12	29	Sodium lauryl sulfate (acetone washed)	127.41 mg
171.00	30	Purified water	~171
QS	31	Glucose liquid	QS to 1 L

MANUFACTURING DIRECTIONS

Do not expose this preparation during manufacturing to direct sunlight. Riboflavin is sensitive to light. Add 83.7 mL of purified water to a stainless-steel-jacketed tank. Add calcium hypophosphite, calcium lactate, parabens, and benzoic acid. Heat mixture to 60°C with agitation. Shut off mixer, and wash tank free of all powders with 25.9 mL purified water. Heat to and maintain a maximum temperature of 100°C until solution is complete. Do not agitate. Avoid loss of water through evaporation. Cover opening of tank. After solution occurs, take sample from bottom of tank and examine for clarity. Solution must be clear. Add acid hypophosphorous (if used) with mixing. Turn off heat and add 222.0 g glucose and start agitator. (*Caution:* Use CO₂ cover throughout; wherever water is used, it should be CO₂-saturated water.) Dissolve ferrous gluconate in 7.4 mL water CO₂ saturated by heating. Add 278 g glucose with mixing. Add and dissolve sugar. Allow solution to cool to 35°C and mix

well. To 29.6 mL water add and dissolve nicotinamide, riboflavin, D-pantothenyl alcohol, vitamin B12, pyridoxine, and thiamine. Mix until solution is complete, and add to tank. Dissolve by heat, if necessary. Charge raspberry blend flavor and chocolate flavor into tank. Charge saccharin into tank, and mix until dissolved. Charge ascorbic acid into tank, and mix well. Charge caramel into tank, and mix well. Dissolve citric acid in 3 mL water, and add this solution to above. Heat corn oil to 50 to 60°C, and add and dissolve BHA. Be sure the BHA is completely dissolved before continuing. Cool to room temperature. While cooling oil mixture, saturate with CO₂ and maintain heavy CO₂ coverage for balance of operation. Set aside a small amount of this mixture as a rinse for the vitamin A and viosterol containers in previous step. Add vitamin A palmitate and viosterol to the cool corn oil mixture, rinsing the containers with the oil reserved earlier. Add the rinse to the bulk, and mix well. Add the acacia to the oil mixture with good mixing. Dissolve sodium lauryl sulfate in 3 mL

CO₂-saturated purified water. To avoid excessive foaming, do not bubble CO₂ gas through the water/sodium lauryl sulfate solution. Add the sodium lauryl sulfate solution to the oil mixture, and stir to a thick creamy emulsion. Add 7.56 g glucose to the emulsion with mixing. Blend 13.33 mL CO₂-saturated purified water with 77.04 g glucose, and add emulsion with stirring. Recycle primary emulsion back into the holding tank while setting mill. Homogenize until all oil globules are less than 8 μm in diameter using colloid

mill with a very fine setting. After setting mill, *sample*. Do not change mill setting after removing sample unless samples are unacceptable. Add primary emulsion to syrup solution with mixing; add glucose QS to 965 mL, and mix well. Allow to stand overnight to vent entrapped air. Adjust the volume to 1 L using glucose or glucose and CO₂-saturated water. Strain through 149-μm aperture or similar screen into clean reserve tank, and recheck volume.

Multivitamin and Mineral Tablets

Bill of Materials			
Scale (per tablet)	Item	Material Name	Quantity/1000 Tablets (g)
4000 IU/400 IU	1	Vitamin A/vitamin D crystals (500,000 A/50,000 D per g) (25% excess)	10.00
40.00 mg	2	Vitamin A acetate (powder; 500 MA) (20% excess)	50.00
10.00 mg	3	Thiamine hydrochloride (10% excess)	11.00
5.00 mg	4	Riboflavin	5.00
100.00 mg	5	Nicotinamide niacinamide (white powder)	100.00
200.00 mg	6	Ascorbic acid (white powder) (10% excess)	220.00
20.00 mg	7	Calcium pantothenate (dextro) (30% excess)	26.00
5.00 mg	8	Pyridoxine hydrochloride	5.00
7.33 mg	9	Povidone (K-29–32) ^a	7.33
29.16 mg	10	Anhydrous refined alcohol isopropyl	29.16
24.20 mg	11	Talc powder	24.20
6.07 mg	12	Magnesium stearate (impalpable powder)	6.07
4.75 mg	13	Stearic acid (fine powder)	4.75
10.0 mg	14	Iron, use; iron sulfate (dried)	31.26
1.00 mg	15	Copper ^a	1.00
0.15 mg	16	Iodine ^a	0.15
1.00 mg	17	Manganese ^a	1.00
5.00 mg	18	Magnesium ^a	5.00
1.50 mg	19	Zinc ^a	1.50
0.10 mg	20	Cobalt; use cobalt sulfate	0.47
5.00 mg	21	Potassium; use potassium sulfate	11.14
0.20 mg	22	Molybdenum; use sodium molybdate (dihydrate)	0.50
6.00 µg	23	Vitamin B12; use cyanocobalamin (1000 µg/g oral powder in gelatin; 5% excess)	6.30

^a Provided as mineral mix (includes 3% excess).

Bill of Materials			
Scale (mg/Tablet)	Item	Material Name	Quantity/1000 Tablets (g)
13.85	1	Copper sulfate	14.28
0.01175	2	Calcium iodate monohydrate	0.01212
0.1228	3	Manganese sulfate monohydrate	0.1267
0.1480	4	Zinc sulfate (pure dry powder)	0.1526

Grind copper sulfate, calcium iodate, manganese sulfate, and zinc sulfate through Fitz mill screen 0 band (high speed, impact forward).

MANUFACTURING DIRECTIONS

Vitamin A is susceptible to destruction by oxidation and also excessive exposure to actinic light and moisture. Compression of this tablet should be done where relative humidity is less than 40%. Protect granulation with CO₂ if material is not to be compressed soon after granulation. Hand screen vitamin A and D crystals and vitamin A acetate through 1.2-mm aperture screen. Load into mass mixer (screen using 1.2-mm aperture screen, if necessary) Thiamine HCl, riboflavin, nicotinamide, ascorbic acid, calcium pantothenate, pyridoxine HCl and the vitamin A and D mix from above. Blend for 10 minutes. Dissolve Povidone in alcohol (~26 mL). Add Povidone solution to

blended materials, and mix for 5 minutes. Scrape mixer, then add alcohol to mass (~11 mL). Pass wet mass through a 15.88-mm aperture (or similar), band-fitted to rotary granulator. (*Note:* Wet mass can set hard; therefore, granules should be spread quickly onto trays.) Dry the granulation at 49°C until LOD is less than 1.0%. Pass the dried granulation through a 1.2-mm aperture screen fitted to an oscillating granulator. Mill the talc (item 11), magnesium stearate, stearic acid, iron sulfate, mineral mix, cobalt sulfate, potassium sulfate, and sodium molybdate through a 595-µm-aperture screen at high speed, impact forward. Load half of the granulation into a suitable blender; add mineral mix and cyanocobalamin oral powder. Add balance of granulation and blend for 30 minutes. Compress and coat using a sealing subcoating of polyvinylpyrrolidone (PVP) (see Appendix), followed by HPMC coating solution and clear methocel gloss.

Multivitamin Chewable Tablets for Children

Bill of Materials			
Scale (per tablet)	Item	Material Name	Quantity/1000 Tablets (g)
3500 IU	1	Vitamin A acetate (dry powder; 500,000 IU/g) (BASF)	7.00
1.20 mg	2	Thiamine mononitrate (BASF)	1.20
1.20 mg	3	Riboflavin (BASF)	1.20
20.00 mg	4	Nicotinamide	20.00
1.80 mg	5	Pyridoxine hydrochloride (BASF)	1.80
6.50 mg	6	Cyanocobalamin (dry powder; 0.1%), BASF	6.50
60.00 mg	7	Ascorbic acid (powder) (BASF)	60.00
5.00 mg	8	Vitamin D3 acetate (dry powder; 100,000 IU/g) (BASF)	5.00
31.00 mg	9	Vitamin E acetate (dry powder, SD 50) (BASF)	31.00
200.00 mg	10	Sorbitol (crystalline)	200.00
200.00 mg	11	Sucrose (crystalline)	200.00
20.00 mg	12	Kollidon® VA 64	20.00
1.00 mg	13	Aerosil® 200	1.00
30.00 mg	14	Orange flavor (dry powder)	30.00
6.00 g	15	Raspberry flavor (dry powder)	6.00
3.00 mg	16	Passion fruit flavor (dry powder)	3.00
2.00 mg	17	Cyclamate sodium	2.00

MANUFACTURING DIRECTIONS

Mix all ingredients, pass through an 0.8-mm sieve, and press with medium to high compression force (20 kN). Compress 575 mg using 12-mm biplanar punches.

Multivitamin Drops

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
13,600 IU	1	Vitamin A palmitate (1.7 MM IU/g) (BASF)	8.00
5,200 IU	2	Vitamin D3 (40 MM IU/g)	0.13
5.00	3	Vitamin E acetate (BASF)	5.00
150.0	4	Cremophor EL (or Cremophor RH 40)	150.00
2.00	5	Parabenes (Methyl and propyl)	2.00
525.00	6	Water purified	525.00
4.00	7	Thiamine hydrochloride (BASF)	4.00
2.00	8	Riboflavin 5-phosphate sodium	2.00
2.00	9	Pyridoxine hydrochloride (BASF)	2.00
2.00	10	Nicotinamide	2.00
0.20	11	Sodium bisulfite	0.20
200.00	12	Propylene glycol	200.00
QS	13	Water purified	10.00
QS	14	Hydrochloric acid	QS

MANUFACTURING DIRECTIONS

Heat mixture of items 1 to 4 to about 60°C; stir strongly, and slowly add solution of items 5 and 6 (60°C). To the

obtained clear solution, add solution of items 7 to 13. Adjust the pH with item 14 to about 4 and QS to volume.

Multivitamin Effervescent Granules

Bill of Materials			
Scale (mg/Sachet)	Item	Material Name	Quantity/1000 Sachet (g)
2.60	1	I. Thiamin hydrochloride (BASF)	0.26
3.00	2	Riboflavin (BASF)	0.30
11.00	3	Nicotinamide	1.10
2.50	4	Pyridoxine hydrochloride (BASF)	0.25
15.00	5	Calcium D-pantothenate (BASF)	1.50
200.00	6	Ascorbic acid (powder) (BASF)	20.00
500.00	7	Citric acid	50.00
1300.00	8	Sucrose	130.00
800.00	9	Fructose	80.00
200.00	10	Kollidon® CL-M	20.00
250.00	11	Flavors	25.00
20.00	12	Cyclamate sodium	2.00
1.00	13	Saccharine sodium	0.10
150.00	14	Kollidon® VA 64	15.00
350.00	15	Isopropanol	35.00
5000 IU	16	Vitamin A acetate (dry powder; 325,000 IU/g CWD) (BASF)	1.50
800 IU	17	Vitamin D3 (dry powder; 100,000 IU/g CWD) (BASF)	0.80
21.00	18	Vitamin E acetate (dry powder; 50%)	2.10
0.0660	19	Cyanocobalamin (gelatin-coated; 0.1%) (BASF)	0.66
400.00	20	Sodium bicarbonate	40.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 13 with solution of items 14 and 15. Pass through an 0.8-mm sieve, drywell, and mix with items 16 to 20. Fill 4 g in sachets.

Multivitamin Effervescent Tablets with Beta Carotene

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.00	1	Thiamine mononitrate (BASF)	2.00
2.00	2	Riboflavin (BASF)	2.00
2.00	3	Pyridoxine hydrochloride (BASF)	2.00
22.00	4	Nicotinamide	22.00
11.00	5	Calcium D-pantothenate (BASF)	11.00
400.00	6	Tartaric acid (powder)	400.00
300.00	7	Lactose monohydrate	300.00
100.00	8	Corn starch	100.00
3.00	9	Corn starch	3.00
50.00	10	Water	50.00
23.00	11	Beta carotene (dry powder; 10% CWD; food grade) (BASF)	23.00
6.00	12	Cyanocobalamin (powder; 0.1%) (BASF)	6.00
85.00	13	Ascorbic acid (powder) (BASF)	85.00
40.00	14	Vitamin E acetate (dry powder; 50%)	40.00
600.00	15	Sodium bicarbonate	600.00
80.00	16	Flavors	80.00
QS	17	Saccharin sodium	QS

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 6 with solution of items 9 and 10 prepared at 70°C. Dry and sieve; add items 11 to 17, pass through a 0.4-mm sieve, and press with high

compression force at maximum 30% of relative atmospheric humidity. Compress 1.63 g using 16-mm biplanar punches.

Multivitamin Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
13.00	1	Thiamine mononitrate (BASF)	13.00
4.00	2	Riboflavin (BASF)	4.00
11.00	3	Pyridoxine hydrochloride (BASF)	11.00
66.00	4	Nicotinamide	66.00
17.00	5	Calcium D-pantothenate (BASF)	17.00
360.00	6	Tartaric acid (powder)	360.00
550.00	7	Sodium bicarbonate	550.00
300.00	8	Sucrose (crystalline)	300.00
300.00	9	Sucrose (powder)	300.00
35.00	10	Kollidon® 30	35.00
5.00	11	Kollidon® 30	5.00
QS	12	Isopropanol	~80.00
6.00	13	Riboflavin (BASF)	6.00
550.00	14	Ascorbic acid (powder) (BASF)	550.00
20.00	15	Cyanocobalamin (dry powder, 0.1%)	20.00
12.00	16	Vitamin A palmitate (250,000 IU/g dry powder CWD) (BASF)	12.00
60.00	17	Vitamin E acetate (dry powder; 50%)	60.00
80.00	18	PEG-6000 (powder)	80.00
100.00	19	Kollidon® CL	100.00

MANUFACTURING DIRECTIONS

Granulate the mixture of items 1 to 10 with solution of items 11 and 12; dry at 60°C with vacuum. Mix with items

13 to 19, and press with high compression force at maximum 30% of relative atmospheric humidity. Compress 2.5 g per tablet using 20-mm biplanar punches.

Multivitamin Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.50	1	Thiamine mononitrate (BASF)	5.50
5.50	2	Riboflavin (BASF)	5.50
6.50	3	Pyridoxine hydrochloride (BASF)	6.50
60.00	4	Nicotinamide	60.00
30.00	5	Calcium D-pantothenate (BASF)	30.00
200.00	6	Ascorbic acid (powder) (BASF)	200.00
0.20	7	Cyanocobalamin (dry powder, 0.1%)	20.00
30.00	8	Vitamin A acetate (dry powder; 325,000 IU/g CWD) (BASF)	30.00
55.00	9	Vitamin E acetate (dry powder; 50%)	110.00
500.00	10	Citric acid (powder)	500.00
400.00	11	Tartaric acid (powder)	400.00
500.00	12	Sodium bicarbonate	500.00
600.00	13	Ludipress®	600.00
70.00	14	PEG-6000 (powder)	70.00
0.50	15	Saccharin sodium	0.50
40.00	16	Cyclamate sodium	40.00
200.00	17	Sucrose, crystalline	200.00
200.00	18	Fructose	200.00
100.00	19	Flavors (Firmenich)	100.00

MANUFACTURING DIRECTIONS

Mix all components, and sieve through an 0.8-mm screen.
Press with high compression force at maximum 30%

relative atmospheric humidity. Compress 3 g in 20-mm
biplanar punches.

Multivitamin Infant Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
1125 IU	1	Vitamin A palmitate (1.7 MM IU/g) (50% excess)	1.324
416 IU	2	Vitamin D (40 MM IU/g) (cholecalciferol, 25% excess)	0.013
5.00	3	Vitamin E (oily; α -tocopheryl acetate)	5.00
52.50	4	Ascorbic acid (50% excess)	52.50
0.375	5	Thiamine hydrochloride (50% excess)	0.75
0.40	6	Pyridoxine hydrochloride	0.40
8.00	7	Nicotinamide	8.00
0.00125	8	Cyanocobalamine (50% excess)	0.0025
0.82	9	Riboflavin sodium phosphate (5% excess as riboflavin)	0.865
2.50	10	Poloxyl 20 cetostearyl ether (Cetomacrogol 1000)	2.50
12.50	11	Polysorbate 80 (Tween 80)	12.50
0.50	12	Edetate disodium (sodium EDTA)	0.50
3.75	13	Sodium hydroxide	3.75
0.25	14	Saccharin sodium	0.25
300.00	15	Glycerin (glycerol)	300.00
500.00	16	Sorbitol (70% solution)	500.00
50.00	17	Propylene glycol	50.00
1.50	18	Flavor	1.50
3.00	19	Flavor	3.00
1.50	20	Flavor	1.50
—	21	Purified water	QS to 1 L

MANUFACTURING DIRECTIONS

The product is a micro-emulsion and thermolabile. The temperature of solution must not exceed 25°C at the time of processing. Store bulk at temperature 15 to 20°C under nitrogen protection to avoid discoloration and precipitation. Period of storage should not exceed 48 hours prior to filling in the bottle. Check and record pH of item 21 (limit: 5.0 to 6.5), and collect 250.0 g of it in manufacturing vessel. Heat to 90 to 95°C for 10 minutes, then cool to 20 to 25°C. Bubble nitrogen gas into cooled item 21 for 20 minutes. Load 200.0 g of item 21 from first step to the manufacturing vessel. Bubble nitrogen gas during all stages of the process. Charge items 12, 13, 14, 4, 5, 7, 6, 9, and 8, one by one, to the manufacturing vessel while mixing. Check that all materials are dissolved completely.

Solution should be clear. Add item 11 in a separate stainless steel container, and heat to 45°C. Mix items 1, 2, 3, and 10, one by one. Mix for 1 hour at slow speed. Add oil phase preparation to the aqueous phase at a rate of 2 mL per minute while mixing; keep on bubbling nitrogen gas throughout the process. Add items 15 and 16 to the manufacturing vessel one by one while mixing. Keep on bubbling nitrogen gas throughout the process. Add items 18, 19, and 20 in item 17 and add to the manufacturing vessel while mixing. Adjust the volume to 1.0 L using nitrogen-bubbled item 21. Mix for 10 minutes at slow speed without aeration. Check pH (limit: 3.7 to 4.5). Filter the product at 1.5 bar. Recirculate about 100 to 150 mL of product. Transfer the filtered product to the storage vessel under a nitrogen blanket.

Multivitamin Infant Drops

Bill of Materials			
Scale (mg/0.6 mL)	Item	Material Name	Quantity/L
675.00	1	Glycerine, USP (96%)	675.00 g
10.00	2	Nicotinamide niacinamide (white powder) (5% excess)	17.50 g
2.74	3	Riboflavin-5'-phosphate sodium (0% excess)	2.74 g
0.50	4	Methylparaben (powder)	500.00 mg
1.00	5	Benzoic acid	1.00 g
2.10	6	Saccharin sodium (powder)	2.10 g
1.50	7	Thiamine HCl (45% excess)	3.625 g
0.60	8	Pyridoxine HCl	833.34 mg
50.00	9	Ascorbic acid (white powder) (20% excess)	100.00 g
0.257	10	Orange oil terpeneless No. 54125	257.789 mg
0.095	11	Alcohol (ethanol)	95.50 mg
80.00	12	Polysorbate 80	80.00 g
0.186	13	Butylated hydroxyanisole	186.92 mg
400 IU	14	Vitamin D viosterol in corn oil (oleovitamin D) (25% excess)	833.34 mg
5000 IU	16	Vitamin A; use vitamin A palmitate (1,500,000 AU/g) (50% excess ^a)	16.66 g
QS	17	Purified water	329 g
QS	18	Carbon dioxide gas	QS

^a Excess includes 20% manufacturing loss and 30% stability excess.

MANUFACTURING DIRECTIONS

Use carbon dioxide cover at all time, and use stainless steel 316 or higher resistant equipment. Add 300 mL of purified water and the glycerine into a suitable jacketed tank. Start mixing. Add, in this order, nicotinamide, riboflavin-5-phosphate sodium, Aspetoform M, benzoic acid, and saccharin sodium. Continue mixing for balance of process. Heat to 90 to 100°C to dissolve ingredients. In a separate tank, boil at least 15 mL of purified water for at least 15 minutes. Cool while bubbling CO₂ gas into it, and hold at 30°C or lower for use later for making up the volume. Start cooling the main tank. When the temperature reaches 50 to 60°C, start bubbling CO₂ gas through the solution from the bottom of the tank. Continue cooling to 25°C. Continue the CO₂ gas protection for the balance of the process. Add and dissolve thiamine HCl, pyridoxine HCl, and ascorbic acid. Dissolve orange oil in alcohol and add. Load approximately 5.25 g of Polysorbate 80 into a separate stainless steel container. Heat to 50 to 60°C; add the butylated hydroxyanisole and dissolve with mixing. Remove heat. Add remaining Polysorbate 80 into the container, setting aside a sufficient quantity for rinsing the vitamin containers. Bubble in CO₂

gas while mixing slowly. Stop mixing. Add viosterol and vitamin A palmitate. Rinse bottles with remaining Polysorbate 80, and drain. Mix slowly for at least 30 minutes or longer, if necessary, to provide a clear solution. Continue to bubble CO₂ gas for the entire mixing period. Change CO₂ gas protection on main mixing tank to the top to prevent excessive foaming upon addition of Polysorbate 80 solution. Add Polysorbate 80 solution to the main tank from the bottom of the tank to the top to prevent excessive foaming. Stop mixing. If the volume is less than 1000 mL, adjust the volume with CO₂-saturated purified water made above to 1000 mL; mix for at least 1 hour. In a separate tank, boil at least 115 mL of purified water for at least 15 minutes. Cool while bubbling CO₂ gas into it, and hold at 30°C or lower for use later. Stop mixing. Allow to stand for at least 4 hours to eliminate entrapped CO₂ gas. Readjust volume to 1000 mL with CO₂-saturated purified water; mix for at least 1 hour. Stop mixing. Filter through lint-free paper, and do not use filter aids. Recirculate product back to mixing tank until clear. Flush storage tank with CO₂ gas and continue CO₂ gas protection until product has been filled. Average intake dose is 0.60 mL.

Multivitamin Instant Granules

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Quantity/30 kg (g)
40.00	1	Vitamin A and vitamin D (dry powder + 50,000 IU/g CWD) (BASF)	200.00
5.00	2	Thiamine mononitrate (BASF)	26.00
6.00	3	Riboflavin (BASF)	33.00
22.00	4	Nicotinamide	110.00
4.50	5	Pyridoxine hydrochloride (BASF)	22.00
30.00	6	Calcium D-pantothenate (BASF)	150.00
0.013	7	Cyanocobalamin; use cyanocobalamin (gelatin-coated, 0.1%) (BASF)	66.00
230	8	Ascorbic acid powder (BASF)	1150.00
—	9	Vitamin E acetate dry powder	210.00
4,000	10	Sucrose (finely ground)	20,000.00
1,000	11	Kollidon® CL-M	5000.00
200	12	Orange flavor	1000.00
400	13	Kollidon® VA 64	2000.00
—	14	Ethanol or isopropanol	~7.00 L

MANUFACTURING DIRECTIONS

Pass mixture through an 0.8-mm sieve, and granulate with solution of items 13 and 14 in the fluidized bed. Fill 6 to 12 g of the granules in sachets. If the technology of a

fluidized bed is not available, the dry powders of vitamins A, E, and B12 should be added after granulation of the other components. Suspend 6 to 12 g (= 1 sachet) in a glass of water; corresponds to 2 to 4 RDA of vitamins.

Multivitamin Mineral Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
6.65	1	Acid hypophosphorous (50% pure)	6.65
16.47	2	Calcium hypophosphite	16.47
31.68	3	Calcium lactate (powder)	31.68
1.00	4	Methyl paraben	1.00
0.20	5	Propyl paraben	200.00 mg
1.00	6	Benzoic acid	1.00
150.00	7	Sucrose (granular)	150.00
5.20	8	Ferrous gluconate	5.20
2.00	9	Niacinamide (5% excess)	2.10
0.32	10	Riboflavin-5-phosphate sodium	328.77 mg
1.00	11	D-Pantothenyl alcohol (dexpantenol) (20% excess)	1.20
0.60	12	Vitamin B12 (cyanocobalamin) (35% excess)	810.00 mcg
0.20	13	Pyridoxine hydrochloride	200.00 mg
0.30	14	Thiamine hydrochloride (regular powder) (55% excess)	465.00 mg
4.78	15	Flavor	4.78
1.94	16	Flavor	1.94
0.64	17	Orange oil, terpeneless	642.00 mg
0.21	18	Lime oil, distilled	214.97 mg
4.28	19	Alcohol (190 proof)	4.28
2.50	20	Saccharin sodium	2.50
14.50	21	Acid ascorbic (white powder/EP) (45% excess)	14.50
3.00	22	Caramel (acid proof)	3.00
2.00	23	Anhydrous citric acid (powder/EP)	2.00
0.01	24	Butylated hydroxyanisole (BHA)	10.00 mg
3.39	25	Corn oil	3.39
0.40	26	Vitamin A palmitate (TN, 1.5 MM UA/g) (40% excess)	560.00 mg
0.08	27	Viosterol in corn oil (<i>syn.</i> oleovitamin D; 1000 mD/g; D3 in arachis oil) (40% excess)	112.00 mg
1.50	28	Acacia	1.50
0.12	29	Sodium lauryl sulfate (acetone washed)	127.41 mg
171.00	30	Deionized, purified water	171.00
QS	31	Glucose liquid	QS to 1 L

MANUFACTURING DIRECTIONS

Do not expose this preparation during manufacturing to direct sunlight. Riboflavin is sensitive to light. Add 83.7 mL of purified water to a stainless-steel-jacketed tank. Add calcium hypophosphite, calcium lactate, parabens, and benzoic acid. Heat mixture to 60°C with agitation. Shut off mixer and wash tank free of all powders with 25.9 mL purified water. Heat mixture to and maintain a maximum temperature of 100°C until solution is complete. Do not agitate. Avoid loss of water through evaporation. Cover opening of tank. After solution occurs, take sample from bottom of tank and examine for clarity. Solution must be clear. Add acid hypophosphorous (if used) with mixing. Turn off heat and add 222.0 g glucose, and start agitator. (*Caution:* Use CO₂ cover throughout; wherever water is used, it should be CO₂-saturated water.) Dissolve ferrous gluconate in 7.4 mL water CO₂-saturated by heating. Add 278 g glucose with mixing. Add and dissolve sugar. Allow solution to cool to 35°C and

mix well. To 29.6 mL water add and dissolve nicotinamide, riboflavin, D-pantothenyl alcohol, vitamin B12, pyridoxine, and thiamine. Mix until solution is complete, and add to tank. Dissolve by heat, if necessary. Charge flavors into tank. Charge saccharin into tank, and mix until dissolved. Charge ascorbic acid into tank, and mix well. Charge caramel into tank, and mix well. Dissolve citric acid in 3 mL water and add to above. Heat corn oil to 50 to 60°C and add and dissolve BHA. Be sure the BHA is completely dissolved before continuing. Cool to room temperature. While cooling oil mixture, saturate with CO₂ and maintain heavy CO₂ coverage for balance of operation. Set aside a small amount of this mixture as a rinse for the vitamin A and viosterol containers above. Add vitamin A palmitate TN and viosterol to the cool corn oil mixture, rinsing the containers with the oil reserved above. Add the rinse to the bulk. Mix well. Add the acacia to the oil mixture with good mixing. Dissolve sodium lauryl sulfate in 3 mL CO₂-saturated purified water. To avoid excessive foaming, do not bubble CO₂ gas through

the water/sodium lauryl sulfate solution. Add the sodium lauryl sulfate solution to the oil mixture and stir to a thick creamy emulsion. Add 7.56 g glucose to the emulsion with mixing. Blend 13.33 mL CO₂-saturated purified water with 77.04 g glucose, and add emulsion with stirring. Recycle primary emulsion back into holding tank while setting mill. Homogenize until all oil globules are less than 8 µm in

diameter using colloid mill with a very fine setting. Add primary emulsion to syrup solution with mixing; add glucose QS to 965 mL, and mix well. Allow to stand overnight to vent entrapped air. Adjust the volume to 1 L using glucose or glucose and CO₂-saturated water. Strain through 149-µm aperture or similar screen into clean reserve tank, and recheck volume. Seal tank under heavy CO₂ until filled.

Multivitamin Oral Gel with Linoleic and Linolenic Acid

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/100 mL (mg)
0.05	1	Evening primrose oil (Epopure®, Prima Rosa/SA)	5.00 mL
0.30	2	Vitamin A palmitate (1.7 KMM IU/g) (BASF)	30.00
0.19	3	Vitamin E acetate (BASF)	19.00
0.00150	4	Vitamin D3 (40 MM IU/g)	150.00 µg
200.00	5	Cremophor RH 40	20.00 g
550.00	6	Water	55.00 g
0.03	7	Thiamine hydrochloride (BASF)	3.00
0.03	8	Riboflavin (BASF)	3.00
0.15	9	Pyridoxin hydrochloride (BASF)	15.00
0.001	10	Cyanocobalamin (crystalline)	10.00 µg
0.001	11	Calcium D-pantothenate (BASF)	10.00
0.005	12	Nicotinamide	50.00
10.00	13	Ascorbic acid (crystalline) (BASF)	1.00 g
140.00	14	Lutrol F 127	14.00 g
50.00	15	Lutrol F 127	5.00 g

MANUFACTURING DIRECTIONS

Prepare mixture of items 1 to 5 and heat to about 65°C. Slowly add the warm water (item 6) (65°C) to the well-stirred mixture as before. Dissolve items 7 to 14 at 20 to 25°C in this clear solution. Cool the obtained solution to

about 5°C, and dissolve the rest of the Lutrol F 127 (item 15). Maintain the cool temperature until the air bubbles escape. A clear yellow gel is obtained. 5 mL of evening primrose oil Epopure® contains 3.5 g linoleic acid and 0.45 g γ-linolenic acid.

Multivitamin Oral Gel Veterinary

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (mg)
18,700 IU	1	Vitamin A palmitate (1.7 MM IU/g) (BASF)	110.00
1.06	2	Vitamin E acetate (BASF)	1060.00
0.50	3	Butylhydroxytoluene	500.00
20.00	4	Cremophor RH 40	20.00 g
725.00 g	5	Water	725.00 g
0.355	6	Thiamine hydrochloride (BASF)	355.00
0.035	7	Riboflavin (BASF)	35.00
0.177	8	Pyridoxin hydrochloride (BASF)	177.00
0.035	9	Cyanocobalamin (gelatin-coated, 1%)	35.00
0.353	10	Nicotinamide	353.00
0.035	11	Folic acid	35.00
0.353	12	Dexpanthenol (BASF)	353.00
0.30	13	EDTA sodium	300.00
0.438	14	Ferrous sulfate (7H ₂ O)	438.00
0.638	15	Manganese chloride (4H ₂ O)	638.00
0.115	16	Potassium iodide	115.00
50.00	17	Kollidon® 90 F	50.00 g
100.00	18	Lutrol F 127	100.00 g
100.00	19	Lutrol F 127	100.00 g

MANUFACTURING DIRECTIONS

Heat mixture of items 1 to 4 to about 60°C to obtain a clear solution. Slowly add the water (item 5) to the well-stirred solution. Dissolve items 6 to 16 and item 17

separately in this mixed solution at room temperature, cool to about 6°C, add item 19, and stir until all Lutrol F 127 is dissolved. Maintain the cool temperature until the air bubbles escape.

Multivitamin Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/100 mL
170 IU	1	Vitamin A palmitate (1.7 million IU/g) (BASF)	10.00
2.00 IU	2	Vitamin D (40 million IU/g)	0.05
1.00	3	Vitamin E acetate (BASF)	100.00
0.02	4	Butylhydroxytoluene	2.00
45.00	5	Cremophor RH 40	4.50 g
100.00	6	Water	10.00 g
450.00	7	Saccharose	45.00 g
2.00	8	Methyl parabene	200.00
0.08	9	Citric acid	80.00
9.60	10	Glycerol	9.60 g
250.00	11	Water	25.00 g
0.15	12	Thiamine hydrochloride (BASF)	15.00
0.15	13	Riboflavin 5'-phosphate sodium	15.00
0.55	14	Nicotinamide	55.00
0.15	15	Pyridoxine hydrochloride (BASF)	15.00
3.00	16	Ascorbic acid (crystalline) (BASF)	300.00
1.00	17	Sorbic acid	100.00
5.00	18	Propylene glycol (Pharma)	5.00 g

MANUFACTURING DIRECTIONS

Mix items 1 through 5 and heat to 60°C. Separately heat item 2 to about 60°C. Mix these two solutions slowly, stirring well to obtain a clear solution. Dissolve items 7 to 9 in the hot solution of items 10 and 11 to obtain a

clear solution. Add to solution above. Add items 12 to 18, and adjust the pH to 4.0 to 4.2. Pass nitrogen through the solution for 10 minutes, and fill under nitrogen cover. Provides 1 to 2 RDA/20 mL.

Multivitamin Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/100 mL (mg)
0.17	1	Vitamin A palmitate (1.7 MM IU/g) (BASF)	17.00
0.001	2	Vitamin D3 (40 MM IU/g)	0.10
0.01	3	Butylhydroxytoluene	1.00
30.00	4	Cremophor RH 40	3.00 g
1.00	5	Parabenes	100.00
170.00	6	Water	17.00 g
0.50	7	Thiamine hydrochloride (BASF)	50.00
0.20	8	Riboflavin phosphate sodium	20.00
0.20	9	Pyridoxine hydrochloride (BASF)	20.00
2.50	10	Ascorbic acid (crystalline) (BASF)	250.00
50.00	11	Water	5.00 g
—	12	Sugar syrup	ad 100 mL

MANUFACTURING DIRECTIONS

Heat mixture of items 1 to 4 to about 65°C. Stir well, and very slowly add item 6 to warm solution (65°C). Mix with

solution of items 7 to 11, and add item 12 to make up the volume. (*Note:* Parabenes are generally a 1:10 ratio of methylk and propyl paraben.)

Multivitamin with Beta-Carotene Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.85 IU	1	Vitamin A acetate (dry powder; 500,000 IU/g)	5.47
5.00	2	Beta-carotene; use beta-carotene dry powder (Betavit®, 10%)	50.00
15.34	3	Thiamine mononitrate	15.34
4.13	4	Riboflavin	4.13
50.00	5	Nicotinamide	50.00
8.23	6	Calcium D-pantothenate	8.23
5.00	7	Pyridoxine hydrochloride	5.00
0.04	8	Cyanocobalamin; use gelatin-coated cyanocobalamin (1%)	4.00
0.04	9	D-biotin; use 1% trituration	4.00
0.38	10	Folic acid	0.38
165	11	Ascorbic acid	165
327	12	Vitamin D3 (dry powder; 100,000 IU/g)	3.27
122.00	13	Vitamin E acetate (dry powder; SD 50)	122.00
0.41	14	Phytomenadione; use phytomenadione dry powder (5% GFP)	0.82

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with high compression force. Compress 432 mg in 12-mm biplanar punches.

Multivitamin Tablets with Beta-Carotene

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1.00	1	Beta-carotene; use beta-carotene dry powder (Betavit®, 10%)	10.00
2.00	2	Thiamine mononitrate (BASF)	2.00
2.00	3	Riboflavin (BASF)	2.00
16.00	4	Nicotinamide	16.00
11.00	5	Calcium D-pantothenate (BASF)	11.00
2.00	6	Pyridoxine hydrochloride (BASF)	2.00
0.06	7	Cyanocobalmine; use cyanocobalamin dry powder (0.1%)	6.00
85.00	8	Ascorbic acid (powder) (BASF)	85.00
31.00	9	Vitamin E acetate (dry powder; SD 50)	31.00
321.00	10	Ludipress®	321.00
7.00	11	Kollidon® VA 64	7.00
3.00	12	Magnesium stearate	3.00
7.00	13	Orange flavor	7.00
2.00	14	Saccharin sodium	2.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, mix, and press with medium compression force. Compress 508 mg using 12-mm planar punches.

Multivitamin and Beta-Carotene Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
7.00	2	Beta-carotene; use beta-carotene dry powder (10%, Pharma) (BASF)	70.00
2.20	3	Thiamine mononitrate (BASF)	2.20
2.20	4	Riboflavin (BASF)	2.20
6.50	5	Nicotinamide	6.50
11.50	6	Calcium D-pantothenate (BASF)	11.50
2.20	7	Pyridoxine hydrochloride (BASF)	2.20
0.06	8	Cyanocobalmine; use cyanocobalamin dry powder (0.1%)	6.00
85.00	9	Ascorbic acid (powder) (BASF)	85.00
32.00	10	Vitamin E acetate (dry powder; SD 50)	32.00
210.00	11	Ludipress®	210.00
7.00	12	Kollidon® VA 64	7.00
3.00	13	Magnesium stearate	3.00
7.00	14	Orange flavor	7.00
2.50	15	Saccharin sodium	2.50

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, mix, and press with medium compression force. Compress 448 mg using 12-mm planar punches.

Multivitamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Thiamine mononitrate (powder), USP (5% excess; 5 to 10%)	10.50
5.00	2	Riboflavin, USP	5.00
100.00	3	Nicotinamide niacinamide (white powder), USP	100.00
200.00	4	Ascorbic acid, use sodium ascorbat (microcrystalline) (2% excess)	229.47
20.00	5	Calcium pantothenate; use calcium pantothenate racemic (20% excess)	48.00
5.00	6	Pyridoxine hydrochloride, USP	5.00
6.10	7	Povidone (PVP K-25), USP	6.10
—	8	Alcohol dehydrated (200 proof), USP	25.00 mL
21.90	9	PEG-8000, NF	21.90
25,000 IU	10	Vitamin A (275,000 IU ^a) (20% excess)	7.50 mg
400 IU	11	Vitamin D as D2 powder (850 mD ^a)	1.77
6.00	12	Vitamin B12 oral powder in gelatin (5% excess)	6.30
16.00	13	PEG-8000 (milled), NF	16.00
5.30	14	Magnesium stearate	5.30
23.20	15	Talc	23.20

^a Adjust quantities according to regulatory allowance for OTC label.

MANUFACTURING DIRECTIONS

Vitamin A is susceptible to destruction by oxidation and also excessive exposure to actinic light and moisture. Oxidation and destruction are catalyzed by traces of copper and other heavy metals. Dry granulation and compression of this tablet should be done where relative humidity is less than 40%. Protect with CO₂ at blending and storage stages. Charge the following into a suitable mixer (screen if necessary): thiamine mononitrate, riboflavin, nicotinamide, sodium ascorbate, calcium pantothenate, and pyridoxine HCl. Dissolve the PVP (item 7) in approximately 16 mL alcohol. Add PVP solution to the powders from first step, and QS with alcohol to mass. Granulate the mass through a 4-mesh (4.76-mm aperture, or similar) screen. Dry at 50°C until the LOD is below 1.0%. Grind to 16 mesh (1.2 mm, or similar). Melt the PEG-8000 (item 10), and incorporate vitamins A and D with thorough agitation. Mix until mass

cools and becomes granular. Screen through a 16-mesh (1.2-mm aperture, or similar) screen, and grind coarse material through a Fitz mill, or similar, No. 2 band (1.59-mm aperture, or similar) at slow speed or a 16-mesh (1.2-mm aperture, or similar). Reserve for lubrication. Mix milled PEG-8000 (item 13) with talc and magnesium stearate, and pass through a Fitz mill, using a 60-mesh (250-μm aperture, or similar) screen (impact forward, high speed). If a Fitz mill is unavailable, pass the mixture through a 30-mesh (595-μm aperture, or similar) screen. Load base granulation into a mixer along with vitamin B12, the mixture from above, and the PEG-coated vitamin A and D mixture from the first step. Blend thoroughly. Store dry mixed granulation with CO₂ protection. Compress. Apply a PVP subcoat, a CAP-carbowax or other aqueous coating and finish with a polish coat. (See Appendix.)

Multivitamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Riboflavin	10.00
100.00	2	Niacinamide (white powder)	100.00
5.00	3	Pyridoxine hydrochloride (15% excess)	5.75
15.00	4	Thiamine mononitrate (powder) (5% excess)	15.75
500.00	5	Ascorbic acid, EP	500.00
100.00	6	Lactose	100.00
40.00	7	Povidone (K-29–32)	40.00
100.00	8	Cellulose microcrystalline (Avicel™ PH101)	100.00
—	9	Alcohol SD 3A (200 proof)	QS
20.00	10	Calcium pantothenate; use racemic calcium pantothenate, USP (80 mesh; 15% excess)	46.00
11.50	12	Magnesium oxide (light powder calcined)	11.50
500.00	13	Ascorbic acid	500.00
3.83	14	Povidone (K-29–32)	3.83
—	15	Alcohol SD 3A (200 proof)	QS
4.00 µg	16	Vitamin B12; use vitamin B12 oral powder in gelatin (15% excess)	4.60
28.00	17	Acid stearic	28.00
9.60	18	Magnesium stearate	9.60

MANUFACTURING DIRECTIONS

Dry-blend the riboflavin, niacinamide, pyridoxine hydrochloride, thiamine mononitrate, ascorbic acid (item 5), and lactose for 10 minutes. Dissolve the Povidone (item 7) in 75 mL of alcohol (item 9). While mixing in mass mixer, add the Povidone solution to mass, and continue mixing for 10 minutes, or until a satisfactory granule mass is obtained. Additional alcohol may be added, if required. Granulate the mass through a 15.9-mm screen using a comminuting mill (knives forward, slow speed) or a 4-mm screen on an oscillating granulator. Dry the granules between 41 and 49°C in a hot air oven (for approximately 8 hours) or fluid-bed dryer until moisture content is below 1.5%. Dry-screen the granule through a 1-mm screen on an oscillating granulator. Dry-blend the calcium pantothenate and magnesium oxide in a suitable mixer for 10 minutes. Dissolve the Povidone

(item 14) in 20 mL alcohol (item 15). While mixing, add the Povidone solution, and mix to produce a suitable mass. Additional alcohol may be added, if required. Granulate the mass through a 15.9-mm aperture screen using a comminuting mill (knives forward, slow speed) or a 4-mm screen on an oscillating granulator. Dry the granule at 45°C in a hot air oven until moisture content is below 1.5%. Dry-screen granule through a 1.0-mm screen on an oscillating granulator. Mix the two granules made separately in a suitable mixer. Add vitamin B12 powder, and blend for 10 minutes. If necessary, screen the stearic acid and magnesium stearate through a 250-µm screen. Add the remainder of the granule together with the magnesium stearate and stearic acid to the mixer and blend for 10 minutes. Compress, and coat. (See Appendix.)

Multivitamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Riboflavin	10.00
100.00	2	Niacinamide (white powder)	100.00
5.00	3	Pyridoxine hydrochloride (15% excess)	5.75
15.00	4	Thiamine mononitrate (powder) (5% excess)	15.75
40.00	7	Povidone (K-29-32)	40.00
25.00	8	Povidone (K-29-32)	25.00
—	9	Alcohol SD 3A (200 proof)	QS
13.50	10	Stearic acid (fine powder)	13.50
2.70	11	Magnesium stearate	2.70

MANUFACTURING DIRECTIONS

Mill the niacinamide, riboflavin, pyridoxine hydrochloride, and thiamine mononitrate through a 500- μ m screen on a comminuting mill (impact forward, slow speed). Load screened material from previous step into a mass mixer, add the Povidone (item 7) and the cellulose microcrystalline, and dry blend for 5 to 15 minutes. While mixing in the mass mixer, add alcohol (item 9) to mass, and continue mixing for 10 minutes or until a satisfactory granule mass is obtained. If necessary, granulate the mass through a 15.9-mm screen using a comminuting mill (knives forward, slow speed) or a 4-mm screen on an oscillating granulator. Dry the granule between 41 and 49°C in a hot air oven (for approximately 8 hours) or fluid-bed dryer until moisture

content is below 1.5%. Dry-screen the granules through a 1.0-mm screen on an oscillating granulator. Load ascorbic acid and Povidone (item 8) into the mixer and dry-blend for 10 minutes. While mixing, add 15 mL of alcohol (item 9), and mix until a satisfactory mass is formed, adding more alcohol if necessary. If necessary, screen through a 4.00-mm screen and load onto trays. Dry at 49°C for 8 hours. Dry screen the granules through a 1.0-mm aperture screen on an oscillating granulator. Screen the magnesium stearate and stearic acid through a 500- μ m aperture screen. Mix the two granules, add the screened lubricants, and blend for 20 minutes. Coat with a protective subcoat, a color coat, and a polish coat (see Appendix).

Multivitamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Vitamin A acetate (dry powder; 500,000 IU/g) (BASF)	10.00
2.20	2	Thiamine mononitrate	2.20
2.20	3	Riboflavin	2.20
16.50	4	Nicotinamide	16.50
11.50	5	Calcium D-pantothenate	11.50
2.20	6	Pyridoxine hydrochloride	2.20
6.00	7	Cyanocobalamin (dry powder, 0.1%)	6.00
85.00	8	Ascorbic acid (powder)	85.00
31.00	9	Vitamin E acetate (dry powder; SD 50)	31.00
321.00	10	Ludipress ^{®a}	321.00
21.00	11	Kollidon [®] VA 64	21.00
3.00	12	Magnesium stearate	3.00
7.20	13	Orange flavor	7.20
2.50	14	Saccharin sodium	2.50

^a Can be replaced with 300 g of microcrystalline cellulose (Vitacel[®]).

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, mix, and press with medium compression force (15 kN). Compress 500 mg in 12-mm biplanar punches.

Multivitamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.00	1	Thiamine hydrochloride	2.20
2.20	2	Riboflavin	2.20
11.00	3	Calcium D-pantothenate	11.00
2.20	4	Pyridoxine hydrochloride	2.20
300.00	5	Mannitol	300.00
20.00	6	Kollidon [®] 30 or Kollidon [®] VA 64	20.00
—	7	Isopropanol	~80
5000 IU vitamin A 500 IU vitamin D	8	Vitamin A and vitamin D; use crystallites of vitamin A acetate + vitamin D3 dry powder (500,000 + 50,000 IU/g) (10% excess)	11.00
31.00	9	Vitamin E acetate (dry powder; SD 50)	31.00
0.06	10	Cyanocobalamin; use gelatin-coated cyanocobalamin (0.1%)	6.00
80.00	11	Ascorbic acid (crystalline)	80.00
20.00	12	Nicotinamide	20.00
65.00	13	Avicel [™] PH101	65.00
7.00	14	Orange flavor	7.00
2.00	15	Saccharin sodium	2.00
3.00	16	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 5 with solution of items 6 and 9. Pass through an 0.8-mm sieve, mix with items 8

to 16, and press with medium compression force. Compress 560 mg in 12-mm biplanar punches.

Multivitamin Tablets for Dogs

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2000 IU Vitamin A 200 IU Vitamin D	1	Vitamin A + vitamin D3 (dry powder; 500,000 + 50,000 IU/g)	4.00
0.50	2	Thiamine mononitrate	0.50
0.70	3	Riboflavin	0.70
5.00	4	Nicotinamide	5.00
1.00	5	Calcium D-pantothenate	1.00
0.50	6	Pyridoxine hydrochloride	0.50
0.50	7	Cyanocobalamin (gelatin-coated, 1%)	0.50
0.05	8	Folic acid	0.05
20.00	9	Choline bitartrate	20.00
20.00	10	Vitamin E acetate (dry powder, SD 50)	20.00
196.00	11	Ludipress®	196.00
2.00	12	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with low compression force. Compress 250 mg using 8-mm biplanar punches.

Multivitamin and Fluoride Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1.20	1	Riboflavin; use coated riboflavin (25% excess)	5.28
0.30	2	Folic acid (powder)	0.31
1.00	3	Fluoride; use sodium fluoride (powder)	2.21
19.50	4	Starch (Bright Yellow 2 LA)	19.50
1.05	5	Pyridoxine; use pyridoxine hydrochloride (6% excess)	4.02
1.05	6	Thiamine HCl; use coated thiamine mononitrate (5% excess)	3.21
13.50	7	Niacin; use nicotinamide	40.20
4.50 µg	8	Vitamine B12; use cyanocobalamin oral powder in starch (10% excess)	5.17
20.00	9	Ascorbic acid; use surface-coated ascorbic acid and sodium	21.00
40.00	10	Sodium ascorbate; use surface-coated sodium ascorbate (5% excess)	47.25
7.49	11	Anhydrous citric acid	7.49
15 IU	12	Vitamin E; use vitamin E (<i>d,l</i> - α -tocopheryl) (5% excess)	31.50
400 IU (10 µg)	13	Vitamin D; use vitamin D3 beadlets (25% excess)	0.65
9.36	14	Flavor	9.36
2500 IU or 0.75 mg	15	Vitamin A; use vitamin A palmitate beadlets (500 mU/g), USP (60% excess)	8.25
500.60	16	Sugar (compressible)	500.60

MANUFACTURING DIRECTIONS

Manufacture this product at less than 40% relative humidity and a temperature below 26.7°C. If lumpy, hand screen riboflavin through an 8-mesh screen, and mix with folic acid, sodium fluoride powder and approximately 3.5 g of Bright Yellow starch in a suitable blender until the yellow color of premix is uniform. Cross-feed the premixed items, pyridoxine hydrochloride, thiamine mononitrate, nicotinamide, cyanocobalamin oral powder in starch, ascorbic acid, citric acid, and vitamin E through an 846-µm screen on a comminuting mill (knives forward, medium speed). Transfer the powders to a suitable blender. Clear mill with a part of the compressible sugar, and transfer to the blender. Charge vitamin D3 beadlets, sodium ascorbate, flavor and vitamin A palmitate into the blender. Blend for

10 minutes. Discharge the contents of the blender into polyethylene-lined drums. Pass the remaining compressible sugar through an 846-µm screen on a comminuting mill (knives forward, medium speed). Transfer to the blender. Screen the material from previous step, the magnesium stearate, and the remaining Bright Yellow starch through an 846-µm screen, and transfer to the blender. (*Note:* Mill material not passing through the screen through an 846-µm screen on a comminuting mill at medium speed with knives forward.) Blend for 20 minutes. Discharge blender into polyethylene-lined drums, and weigh for yield. Use precompression, if available, to obtain a tablet with adequate friability. Coat as needed. (See Appendix.)

Multivitamin with Fluoride Infant Drops

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
8.00	1	Niacin; use niacinamide (5% excess)	8.332
0.60	2	Riboflavin, USP; use riboflavin-5'-phosphate sodium (2% excess)	0.83
0.50	3	Methyl paraben	0.50
1.00	4	Benzoic acid	1.00
5000 IU	5	Vitamin E; use <i>d</i> - α -tocopheryl PEG-1000 succinate (20% excess)	13.826
400 IU	6	Vitamin D; use viosterol in corn oil (<i>syn.</i> oleovitamin D) (25% excess)	0.522
1500 IU (0.45)	7	Vitamin A palmitate (synthetic A palmitate, 1 MM U/g), USP	1.44
35	8	Ascorbic acid (white powder), USP (33% excess)	46.55
0.50	9	Thiamine hydrochloride (44% excess)	0.72
0.40	10	Pyridoxine; use pyridoxine hydrochloride	0.486
0.25	11	Fluoride; use sodium fluoride (powder)	0.5526
4.013	12	Caramel (acid proof)	4.013
0.257	13	Orange oil terpeneless	0.257
QS	14	Alcohol (ethanol; 190 proof)	10.00 mL
QS	15	Distilled purified water	QS
QS	16	Acid hydrochloric	QS
QS	17	Sodium hydroxide	QS
QS	18	Carbon dioxide gas	QS

MANUFACTURING DIRECTIONS

Use only stainless steel tanks, and minimize vortex formation to prevent aeration. Product attacks glass, so avoid contact with glass. Charge 350 mL of purified water into the stainless-steel-jacketed main tank. Start mixing. Add, in this order, niacinamide, riboflavin, sodium fluoride, methyl paraben, and benzoic acid. Rinse the interior walls of the tank with approximately 16 mL purified water. Continue mixing for the balance of the process. Heat the main tank to 95°C to dissolve ingredients. When the solution is complete, cool below 85°C (range, 80 to 90°C). The main tank will have to be heated to 85°C for this step. Add vitamin E to another tank, if necessary, by heating vitamin E container. Melt vitamin E in the tank. Add viosterol and vitamin A, and heat to 60 to 65°C with mixing. Start bubbling in CO₂. Mix slowly for 10 minutes or longer to produce a clear solution. Start CO₂ gas protection on the main mixing tank, and continue for the balance of the process. With the main batch at 85 to 90°C, add the solution of vitamins E, D, and A at 60 to 65°C, with mixing. The addition may cause the temperature of the main batch to drop below the specified range, so readjust to 85 to 90°C. Mix and maintain at this temperature until solution is complete, after which cool to below

30°C. Add the glycerin with mixing. Adjust the temperature to 25 ± 5°C, and maintain at this temperature before proceeding. Add and dissolve with mixing, in this order, ascorbic acid, thiamine, pyridoxine, and caramel. Rinse the caramel container with ~3 mL of water, and add the rinsings. Rinse the tank inner walls and mixer shaft with approximately 3 mL water. Dissolve the orange oil with mixing in the alcohol and add to solution above. Continue mixing for at least 30 minutes to ensure a homogeneous product. Stop mixing, and take pH (range 3.1 to 3.3). If necessary, adjust with 10% sodium hydroxide or 10% hydrochloric acid, prepared by adding 1 mL hydrochloric acid (reagent-grade) with 3.3 mL purified water. Mix. Stop mixing, and allow to stand for at least 4 hours to eliminate entrapped CO₂ gas. In a properly cleaned separate tank, boil at least 65 mL of purified water for at least 15 minutes. Cool while bubbling CO₂ into it, and hold at 30°C. Adjust pH to the range of 3.1 to 3.3. Filter, using a lint-free paper; do not use filter aids. Recirculate product back to main mixing tank until clear. Flush a storage tank with CO₂ for at least 10 minutes with the CO₂ valve completely open. Filter product into this storage tank. Fill under CO₂ cover.

Multivitamin with Zinc Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Niacin; use niacinamide (white powder)	99.20
750.00	2	Ascorbic acid; use microcrystalline sodium ascorbate ^a	843.68
20.00	3	Vitamin B6; use pyridoxine hydrochloride	34.03
QS	4	Povidone	40.00
15.00	5	Thiamine hydrochloride; use thiamine mononitrate (powder)	17.47
15.00	6	Riboflavin	16.50
20.00	7	Pantothenic acid; use calcium pantothenate	32.60
0.49	8	Folic acid (powder)	0.52
12.00 µg	9	Vitamin B12; use cyanocobalamin oral powder in gelatin 1:1000	15.00
60.00	10	Vitamin E (<i>d,l</i> - α -tocopherol acetate)	60.00
—	11	Alcohol SD 3A (200 proof)	138 mL 23 mL
22.50	12	Elemental zinc (pure zinc sulfate powder)	55.61
4.00	13	Povidone	4.00
—	14	Alcohol SD 3A (200 proof)	4 mL
—	15	Alcohol SD 3A (200 proof)	9 mL
10.80	16	Magnesium stearate	10.80
40.00	17	Cellulose microcrystalline	40.00
3.20	18	Silicon dioxide colloidal	3.20
6.00	19	Colloidal silicon dioxide	6.00

^a May use ascorbic acid (750.00 g) instead. The quantity of Povidone is reduced to 6.34 g, and the amount of alcohol SD used is adjusted.

MANUFACTURING DIRECTIONS

Mill niacinamide, sodium ascorbate, pyridoxine, Povidone (item 4), and thiamine through a comminuting mill with hammers (impact forward) at high speed and fitted with a 0 band (686-µm aperture, or similar) screen. Charge millings into mass mixer. Screen riboflavin, calcium pantothenate, folic acid, vitamin B12, and vitamin E through 840-µm screen. Charge into mass mixer, and dry mix for 5 to 10 minutes. Add 89 mL alcohol to powder while mixing. Add additional alcohol, if required (approximately 49 mL), to achieve satisfactory granulation. Pass wet mass through 5/8-inch band (15.88-mm aperture, or similar) screen and spread out on paper-lined trays. Dry granulation at 49°C, and dry until LOD is not more than 1.5%. Sift dry granule through 1.19-mm screen, and coarse grind granule through a No. 2 band (1.59-mm aperture, or similar) screen fitted on a comminuting mill (knives forward, medium speed) to polyethylene-lined drums. Mill zinc sulfate and Povidone through a comminuting mill fitted with a 0 band (686-µm aperture, or similar) screen at high speed with impact (hammers) forward. Charge millings into mass mixer for 5 to 10 minutes. Add 3.3 mL alcohol (item 14) to powders from first step while mixing. If necessary, use additional alcohol

(up to 0.83 mL) to achieve satisfactory granulation. Granulate wet mass through 5/8-inch band (15.88-mm aperture, or similar) screen, and spread out on paper-lined trays. Dry granule at 49°C, and dry until LOD is not more than 1.5%. Sift dry granule through 1.19-mm screen, and coarse grind granule through a No. 2 band (1.59-mm aperture, or similar) screen fitted on a comminuting mill (knives forward, medium speed) and transfer to polyethylene-lined drums. Charge approximately 1/10th of vitamin granulation into blender. Premix magnesium stearate, microcrystalline cellulose, and silicon dioxide in a bowl, and sift through 840-µm screen into blender. Charge another 1/10th more of vitamin granulation into blender, and blend for 5 minutes. Discharge a portion of granulation from the blender, and check for white lumps. If lumps are present, discharge entire granulation through a 1.68-mm aperture screen to break lumps, then return it to blender. Charge zinc granulation into the blender. Charge remaining vitamin granulation into blender, and blend for 15 minutes. Discharge blender into polyethylene-lined drums, tie liners, close and seal drums, and deliver to storage area. Compress and coat (see Appendix).

Naphazoline Eye Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
17.71	1	Acid boric	17.71
1.50	2	Hydroxypropyl methylcellulose 2910 (400 cps)	1.50
0.36	3	Borax (sodium borate)	0.36
1.0	4	Disodium edetate	1.00
0.12	5	Naphazoline hydrochloride	0.12
0.17 mL	6	Benzalkonium chloride; use benzalkonium chloride solution (17%)	0.63 mL
QS	7	Water for injection	QS to 1 L

MANUFACTURING DIRECTIONS

Use thoroughly cleaned and rinsed, steam-jacketed, glass-lined tank or stainless steel tank equipped with a speed-controlled agitator; tank should have a cover. Foaming occurs due to benzalkonium chloride, which concentrates in foam; processing and filling systems should be designed to minimize foaming and allow rapid dissipation of foaming. Charge 80% of final volume of water into mixing tank. Heat deionized water to 90°C. While agitating, add and disperse methylcellulose by slowly sprinkling it on the surface of solution; mix to avoid excessive foaming. Allow 15 minutes for hydration of methylcellulose before discontinuing heating and allowing cooling to 40°C. While agitating, add and dissolve disodium edetate, benzalkonium chloride, boric acid, and sodium borate. Continue cooling to 30 (25 to 30°C); discontinue agitation, and QS to 950 mL with deionized water. Start agitator and mix for at least 15 minutes at 30°C; discontinue agitation and cooling. *Naphazoline hydrochloride concentrate solution:* Dissolve naphazoline hydrochloride in 50 mL of deionized water, sterile-filter

solution through a previously sterilized millipore filter unit containing 0.22-μm membrane. Hold naphazoline solution under aseptic conditions for addition to bulk solution (after it has been autoclaved and cooled). *Prefiltration:* Methylcellulose solutions filter at a slow rate, so use an appropriate filter. Recirculate solution until clear, and transfer to holding or sterilization. *Sterilization and filling:* Use either heat sterilization or sterile filtration. *Heat sterilization:* Sterilize at 112 to 115°C for 60 minutes, cool solution to 25 to 30°C, and aseptically add the sterile naphazoline solution; mix well. Set up a previously sterilized filter and transfer line with 10-μm stainless steel FulFlo filter, or equivalent. Aseptically fill sterile solution into sterilized containers, and apply sterile closure components. *Sterile filtration:* Use Pall cartridge AB 1 NR 7p (pr 8P) with Sartorius Cartridge 526-07 H 1; prepare and steam sterilize the recommended filter units. Aseptically fill the sterilized solution to which the naphazoline solution has been added into each sterilized container, and apply sterile closure.

Neomycin Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
0.50	1	Neomycin sulfate	0.50
50.00	2	Propylene glycol	50.00
5.00	3	Parabenes	5.00
200.00	4	Lutrol F 127	200.00
745.00	5	Water	745.00

MANUFACTURING DIRECTIONS

Dissolve the parabenes and Lutrol F 127 in water heated to about 80°C. Add the propylene glycol, and dissolve neomycin sulfate. Cool to room temperature when the air

bubbles escape. *Alternative:* Dissolve parabenes in hot water, cool to 5 to 10°C, dissolve Lutrol F 127, add propylene glycol, and dissolve neomycin sulfate. Maintain the cool temperature until the air bubbles escape.

Nicotinamide Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Nicotinamide (Degussa)	320.00
160.00	2	Avicel™ PH101	160.00
16.00	3	Kollidon® VA 64	16.00
3.00	4	Magnesium stearate	3.00
3.00	5	Aerosil® 200	3.00

MANUFACTURING DIRECTIONS

With medium compression force, compress 506 mg using 12-mm biplanar punches.

Nicotinic Acid (Niacin) Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Nicotinic acid	200.00
200.00	2	Ludipress®	200.00
5.00	3	Kollidon® CL	5.00
1.50	4	Magnesium stearate	1.50
3.00	5	Aerosil® 200	3.00
10.00	6	PEG-6000	10.00

MANUFACTURING DIRECTIONS

Pass all components through a 0.5-mm sieve. Mix and press with very low compression force. Compress 410 mg using 12-mm biplanar punches.

Nondetergent Neutral Dry Skin Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
60.00	1	Stearic acid	60.00
145.00	2	White petrolatum jelly	145.00
116.00	3	Mineral oil (25 cS)	116.00
10.00	4	Lanolin	10.00
20.00	5	Cetearyl alcohol	20.00
QS	6	Deionized water	QS to 1 kg
14.00	7	Triethanolamine (99%)	14.00
QS	8	Perfume, preservative, color	QS

MANUFACTURING DIRECTIONS

Heat oil and water phases separately to 70°C. Add water phase to oil phase while stirring. Stir to cool, adding

triethanolamine at 60°C and perfuming at 40 to 50°C. This cream serves as a base for drugs, as well. Triethanolamine may be omitted, as it gives a higher pH.

Norephedrine Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
40.00	1	DL-norephedrine hydrochloride	40.00
4.00	2	Parabens	4.00
5.00	3	Saccharin sodium	5.00
3.00	4	Kollidon® 90 F	3.00
500.00	5	Sorbitol solution	500.00
460.00	6	Water	460.00

MANUFACTURING DIRECTIONS

Dissolve the parabens in the hot water, add the sorbitol, cool to room temperature, and dissolve the other components. To prevent discoloration of Kollidon in the solution

during storage, 0.1 to 0.5% cysteine could be added as an antioxidant. Flavors should be added to adjust the taste, as needed.

Nystatin Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
80.00	1	Cetostearyl alcohol	80.00
20.00	2	Poloxyl 20 cetostearyl ether (Cetomacrogol 1000)	20.00
80.00	3	Mineral oil (liquid paraffin)	80.00
2.00	4	Methyl paraben	2.00
100,000 IU	5	Nystatin microfine ^a (30% excess) 5420 IU/mg	24.00
1.00	6	Propyl paraben	1.00
100.00	7	Propylene glycol	100.00
4.86	8	Dibasic sodium phosphate	4.86
2.36	9	Monobasic sodium phosphate	2.36
180.00	10	Petrolatum (soft white paraffin)	180.00
506.00	11	Purified water	506.00

^a Particle size NLT 90% below 45 μm , and 100% below 80 μm .

MANUFACTURING DIRECTIONS

Charge item 3 to the fat melting vessel. Heat to 70°C while stirring. Charge items 10, 1, and 2 to the fat melting vessel while stirring. Mix well, and maintain the temperature at 65 to 70°C. Load 466.0 g of item 11 and item 7 into mixer, and heat to 90°C. Add items 4 and 6 to dissolve, while stirring on manual mode. Mix for 15 minutes at 10 rpm. Cool to 65 to 70°C. Add items 8 and 7 to the parabens solution to dissolve. Mix for 5 to 10 minutes at 10 rpm. Maintain temperature at 65 to 70°C. Take a sample of about 0.40 mL from mixer, and cool to 25°C. Check the pH (6.3 to 7.0). Withdraw 80.0 g of preservative/buffer solution from mixer at 65 to 70°C in a stainless steel container. Cool the solution in stainless steel container to 30 to 35°C. Disperse item 5, carefully using a spatula. Homogenize using homogenizer to make a smooth dispersion. Transfer the molten fat to the mixer containing

the preservative/buffer solution through a stainless steel sieve by vacuum at 0.6 bar while mixing at 10 rpm in manual mode at a temperature of 65°C. Homogenize and mix the cream for 10 minutes at low speed (10 rpm, manual mode) and vacuum of 0.6 bar. Cool to 40 \pm 5°C. Transfer the 104.0 g of drug phase (35 \pm 5°C) to the mixer while mixing. Rinse the stainless steel container of the drug phase with 40.0 g of item 11 (25 to 35°C) and transfer to the mixer while mixing. Rinse the homogenizer and the container with item 11, and transfer the rinsing to the mixer. Mix for 5 minutes. Set the mixer at a mixing speed of 10 rpm (manual mode) and the homogenizer at low speed with a vacuum of 0.6 bar. Mix and homogenize for 15 minutes. Cool to 30°C with mixer speed of 10 rpm and vacuum of 0.6 bar. Transfer the cream to a stainless steel drum.

Nystatin Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity /kg (g)
100,000 IU	1	Nystatin microfina ^a , 5420 IU/mg, 15% excess	21.05
22.00	2	Cetostearyl alcohol	22.00
8.00	3	Paraffin (hard paraffin)	8.00
100.00	4	Mineral oil (liquid paraffin)	100.00
848.95	5	Petrolatum (soft white paraffin)	848.95

^a Particle size NLT 90% below 45 µm, and 100% below 80 µm.

MANUFACTURING DIRECTIONS

Melt items 5, 3, and 2 at 70°C in fat melting vessel. Disperse item 1 in 80.0 g of item 4 in a separate stainless steel container by using a spatula. Pass the dispersion through a homogenizer twice, then transfer the dispersion to the mixer. Rinse the homogenizer and container with 20.0 g of item 4, and transfer the rinsings to the mixer. Homogenize the dispersion at high speed for 15 minutes.

Set the mixer at a temperature of 40 to 45°C. Transfer the molten mass from the fat melting vessel to the mixer at a temperature of 45 to 50°C. Mix for 10 minutes in manual mode and 10 minutes in auto mode at 12 rpm, and vacuum 0.4 to 0.6 bar. Homogenize at high speed for 10 minutes with recirculation. Mix until the temperature of ointment reaches to 28 to 30°C. Transfer the ointment to a stainless steel drum. Keep drum tightly closed.

Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
100,000 IU	1	Nystatin microfine, ^a 5420 IU/mg 20% excess	22.96
4.43	2	Neomycin sulfate ^b	4.43
0.28	3	Gramicidin ^c	0.28
1.00	4	Triamcinolone acetonide micronized	1.00
80.00	5	Cetostearyl alcohol	80.00
20.00	6	Poloxyl 20 cetostearyl ether (Cetomacrogol 1000)	20.00
80.00	7	Mineral oil (liquid paraffin)	80.00
2.00	8	Methyl paraben	2.00
1.00	9	Propyl paraben	1.00
60.00	10	Propylene glycol	60.00
4.86	11	Dibasic sodium phosphate	4.86
2.36	12	Monobasic sodium phosphate	2.36
180.00	13	Petrolatum (soft white paraffin)	180.00
531.86	14	Purified water	531.86

For items 1-3, actual quantity to be calculated per actual potency. Difference in quantity is to be adjusted by purified water.

^a Particle size NLT 90% below 45 µm, and 100% below 80 µm.

^b Particle size NLT 99% below 20 µm, and 75% below 10 µm.

^c Particle size NLT 98% below 50 µm.

MANUFACTURING DIRECTIONS

Load items 13, 5, 6, and 7 in fat melting vessel. Heat to 70°C. Stir to melt. Maintain temperature at 70 to 75°C. Heat 420.0 g of item 14 to 90°C in mixer. Dissolve items 8 and 9 by stirring. Mix for 15 minutes at 10 to 12 rpm. Cool to 65 to 70°C. Dissolve items 11 and 12 in 71.86 g of item 14 at 40 to 45°C in a stainless steel drum. Check the pH (limit: 6.3 to 7.0 at 25°C). Dissolve item 2 into 79.08 g of phosphate solution. The solution should be clear. Disperse item 1 in the neomycin/phosphate solution from above. Homogenize two times with homogenizer (gap setting 1) to make smooth dispersion. Dispersion should be smooth with no lumps. Add 50.0 g of item 10 in a separate stainless steel container and heat to 40 to 45°C, then dissolve item 3 by using a homogenizer. The solution should be clear. Disperse item 4 in the clear solution of gramicidin/propylene glycol by using homog-

enizer. Homogenize until no lumps are present. Maintain temperature at 40 to 45°C. Transfer the melt from step above to the mixer through a stainless steel sieve while mixing at 1012 rpm (manual mode) at a temperature of 65°C. Homogenize at high speed for 10 to 12 minutes at a temperature of 60 to 65°C and a vacuum of 0.6 bar. Scrape the sides and blade. Cool down to 50°C. Transfer the homogenized dispersion to the mixer. Rinse the container with 10.0 g of item 10. Add the rinsing to the mixer, and mix for 10 minutes. Transfer the dispersion to the mixer. Rinse the container with 40.0 g of item 14. Add to the mixer and mix for 10 minutes. Homogenize at high speed for 20 minutes at a temperature of 45°C, mixer speed of 10 to 12 rpm, and vacuum of 0.6 bar. Cool down to 25 to 30°C while mixing. Transfer the cream to a stainless steel drum.

Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
22.96	1	Nystatin microfine ^a	22.96
4.43	2	Neomycin sulfate ^a	4.43
0.28	3	Gramicidin ^a	0.28
1.00	4	Triamcinolone acetonide (micronized)	1.00
100.00	5	Mineral oil (liquid paraffin)	100.00
10.00	6	Syncrowax	10.00
861.33	7	Petrolatum (soft white paraffin)	861.33

^a Actual quantity to be calculated per actual potency. Difference in quantity to be adjusted by use of soft white paraffin.

MANUFACTURING DIRECTIONS

Melt item 7 at 70°C in fat melting vessel. Add item 6 to the melt while mixing. Transfer the melt to the mixer through filters and cool to 40°C while mixing. Add 60.0 g of item 5 in a stainless steel container, and disperse item 1 manually by using a spatula. Homogenize two times with homogenizer (gap setting 1) to make a smooth dispersion, and then transfer to the mixer. Add 20.0 g of item 5 in a stainless steel container, and disperse items 2, 4, and 3 by using the homogenizer to make a smooth

dispersion. Homogenize until no lumps are present. Transfer the dispersion to the mixer. Rinse the homogenizer and stainless steel container with 20.0 g of item 5, and transfer the rinsing to the mixer. Mix for 10 minutes at a mixer speed of 10 rpm and vacuum of 0.4 to 0.6 bar. Set thermostat at 28 to 30°C. Homogenize at high speed, for 20 minutes with recirculation. Mix until the temperature of ointment reaches to 28 to 30°C. Transfer the ointment to a stainless steel drum. Keep drum tightly closed.

Omega Fatty Acids Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
140.00 g	1	Omega fatty acids dry N-3	140.00
140.00 g	2	Avicel™ PH101	140.00
8.40 g	3	Kollidon® VA 64	8.40
2.00 g	4	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with high compression force. Compress 289 mg in 9-mm biconvex punches. The dry powder omega fatty

acids dry N-3 contains 25% fish oil; this fish oil consists of about 30% EPA+DHA. These tablet cores could be coated with an enteric coating of Kollicoat MAE 30 D. (See Appendix for more choices.)

Oral Rehydration Salt (45 mEq)

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
811.90	1	Cerelose powder	811.90
66.57	2	Sodium chloride	66.57
31.82	3	Sodium citrate dihydrate, USP	31.82
70.14	4	Potassium citrate monohydrate (food grade)	70.14
19.57	5	Povidone (PVP K-29-32), USP/BP	19.57
—	6	Alcohol SD 3A (200 proof/190 proof), USP	500.00 mL
—	7	Purified water, USP	50.00 mL

MANUFACTURING DIRECTIONS

Mill the dextrose through a 1.2-mm aperture screen or similar on a comminuting mill (knives forward, medium speed). Individually mill the sodium chloride, sodium citrate, and potassium citrate through a 1.2-mm aperture screen on a comminuting mill (knives forward, medium speed). *Note:* Do not mix the milled items until ready to add them to the dextrose. Charge the powders from steps above into a suitable mass mixer, and mix for 10 minutes. Screen the Povidone through a 1.2-mm aperture screen and transfer to the mixer. Mix all the powders for 5 minutes. Mix 500 mL of alcohol with 50 mL of water and slowly add to the mixer while mixing. Continue to mix for 5 to 10 minutes. Do not

over wet the mass. Granulate the wet mass through a 4.76-mm screen using an oscillating granulator, and spread on stainless steel trays. Dry the granules at 45°C for approximately 16 hours, or until LD is below 0.8%. Turn the granules over after 3 to 4 hours of drying. Screen dried granules through a 840-μm screen. Transfer the fines to a suitable blender. Pass coarse granules through 840-μm screen using an oscillating granulator, and transfer to the blender. Blend for 5 to 10 minutes. Discharge into polyethylene-lined drums. Fill 3.08 g for 100 mL, 7.70 g for 250 mL, and 30.80 g for 1000 mL of reconstituted solution; prorate weights for different volumes.

Pancreatin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
30.00	1	Pancreatin	30.00
308.00	2	Ludipress®	308.00
10.00	3	Kollidon® CL	10.00
2.00	4	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

Mix the components, pass through an 0.8-mm sieve, and press with low compression force. Compress 355 mg using 8-mm biconvex punches. Coat by enteric coating.

Pancreatin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Pancreatin	300.00
290.00	2	Ludipress®	290.00
25.00	3	Kollidon® CL	25.00
3.00	4	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

Mix the components, pass through an 0.8-mm sieve, and press to tablets with low compression force. Compress 615 mg in 11-mm biconvex punches. Coat by enteric coating.

Pancreatin and Cholic Acid Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
130.00	1	Pancreatin	130.00
2.00	2	Cholic acid	2.00
127.00	3	Avicel™ PH101	127.00
56.00	4	Lactose monohydrate	56.00
2.00	5	Magnesium stearate	2.00
3.00	6	Aerosil® 200	3.00

MANUFACTURING DIRECTIONS

Mix the components, and press with high compression force. Compress 324 mg in 9-mm biconvex punches. Coat by enteric coating.

Panthenol Lotion

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L Tablets (g)
26.25	1	D-panthenol (2.5%) ^a	26.25
2.50	2	DL-lactone (pure)	2.50
1.00	3	Sequestrene disodium	1.00
3.00	4	Chlorhexidine hydrochloride (micropowder)	3.00
5.00	5	POEG 300-stearate ^b	5.00
50.00	6	Paraffin oil (low viscosity)	50.00
5.00	7	Polydimethylsiloxane M 350	5.00
3.00	8	Perfume PCV 1155/8	3.00
—	9	Purified water	QS to 1 L

^a Based on 100% content; adjust for assay.

^b POEG 300 is a mixture of monoesters and diesters of polyoxyethylene glycol 300, with palmitic and stearic acids and free polyoxyethylene glycol 300.

MANUFACTURING DIRECTIONS

Aqueous phase: Prepare a solution of DL-lactone (previously liquefied at approximately 100°C) in water. Add the DL-lactone solution to the main part of water at 70°C. Incorporate the D-panthenol (previously liquefied at approximately 45°C). Admix and dissolve sequestrene disodium. *Fatty phase:* Melt at approximately 65°C under stirring POEG 300-stearate, paraffin oil and polydimeth-

ylsiloxane M 350. *Emulsion:* Add the fatty phase at 65°C to the aqueous phase at approximately 45°C. Cool to approximately 36°C while stirring and homogenizing. *Chlorhexidine suspension:* Suspend chlorhexidine in water. *Lotion:* Add the chlorhexidine suspension to the emulsion at approximately 36°C. Stir, homogenize, and deaerate. Finally, add the perfume, homogenize again, and filter.

Panthenol Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
50.00	1	Protegin X	50.00
18.00	2	Cetyl alcohol	18.00
12.00	3	Stearyl alcohol	12.00
40.00	4	Wax (white)	40.00
250.00	5	Wool fat (deodorized)	250.00
130.00	6	Vaseline® (white)	130.00
50.00	7	Almond oil	50.00
150.00	8	Paraffin oil	150.00
50.00	9	D-panthenol	50.00
250.00	10	Deionized water	250.00

MANUFACTURING DIRECTIONS

Place in a heating vessel wool fat, Vaseline, almond oil, and paraffin. Heat and melt the fats together at 80°C with stirring to keep the fatty phase at this temperature until further processing. In a separate container add Protegin X, cetyl alcohol, stearyl alcohol, and white wax; melt these fats with stirring at 80°C. Add to above. The final temperature in the melt should be about 70°C. Keep this temperature until further processing. Transfer D-panthenol into a 10-L container by pouring, then rinse it with hot deionized water. Continue to mix another 5 minutes, check the final weight, and make up for evaporated water (5.67 kg).

Place in kettle, and heat to 70°C while stirring; transfer the melted fatty mass under vacuum (–0.3 mm) through the inline sieve (0.150-mm mesh). After the addition, evacuate again to –0.3 atm. Then, stir for another 15 minutes, and homogenize for 5 minutes under the same conditions. Cool to 30°C (the cooling should occur within 4 hours). When this temperature is reached, continue stirring until the ointment has reached 24 to 26°C. Stop cooling, then evacuate quickly to –0.3 atm, and stir for 5 minutes. Transfer the ointment in a storage vessel, and mix for 5 minutes with electric mixture. Fill the ointment.

Peppermint Rub Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
25.00	1	Sorbital stearate	25.00
15.00	2	Polysorbate 60	15.00
300.00	3	Peppermint oil	300.00
20.00	4	Cetyl alcohol	20.00
40.00	5	Stearic acid	40.00
10.00	6	Triethanolamine (99%)	10.00
2.00	7	Carbopol® 980	2.00
QS	8	Deionized water	QS
QS	9	Preservative, color	QS

MANUFACTURING DIRECTIONS

Hydrate Carbopol in water at 60 to 65°C. Add remaining water phase ingredients. Heat oil and water phases sepa-

ately to 70 to 75°C. Add water phase to oil phase while stirring. Stir to cool, neutralizing at 65°C with triethanolamine.

Phenindion Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Phenindion	50.00
165.00	2	Ludipress®	165.00
2.00	3	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with low compression force. Compress 230 mg in 8-mm biplanar punches.

Phenolphthalein Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Phenolphthalein	200.00
150.00	2	Dibasic calcium phosphate	150.00
11.00	3	Kollidon® 30	11.00
—	4	Isopropanol or ethanol (96%)	QS
19.00	5	Kollidon® CL	19.00
3.00	6	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 and 2 with solution of items 3 and 4, mix with items 5 and 6, pass through an 0.8-mm sieve, and press with low compression force. Compress 385 mg using 9-mm biconvex punches.

Phenolphthalein Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
90.00	1	Yellow phenolphthalein	90.00
64.80	2	Microcrystalline cellulose	64.80
187.20	3	Dicalcium phosphate	187.20
3.60	4	Croscarmellose sodium	3.60
3.60	5	Fumed silica	3.60
7.20	6	Stearic acid	7.20
3.60	7	Magnesium stearate	3.60

MANUFACTURING DIRECTIONS

Screen items 6 and 7 through a 40-mesh sieve. Blend items 1 and 5 in a V-blender for 3 minutes. Add items 2 and 4 to the blender, and mix for 5 minutes. Add item 3 to the

blender, and mix for 12 minutes. Add item 6 and blend for 3 minutes. Add item 7 and mix for another 5 minutes. Compress using 3/8-inch, flat, bevel-edged punches to hardness of 10 kg; average tablet weight is 360 mg.

Phenylpropanolamine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
60.00	1	Phenylpropanolamine hydrochloride, USP	60.00
180.00	2	Calcium sulfate dihydrate	180.00
—	3	Starch paste10%	QS
12.00	4	Starch 1500 (StarX)	12.00
6.00	5	Magnesium stearate	6.00

MANUFACTURING DIRECTIONS

Add starch in 1:10 ratio to cold water, heat to boil with constant stirring until a thick, translucent white paste is formed. Keep it for use in granulation below. Mix the phenylpropanolamine hydrochloride with the calcium sulfate in a Sigma blade mixer for 15 minutes. Add starch paste in sufficient quantity to form a suitable wet mass of desirable consistency. Allow to mix for 30 minutes. Pass

the wet mass through a #14 screen and distribute on drying trays. Dry in a forced-air oven at 49 to 54°C or in a fluid-bed dryer. Pass the dried granules through a #18 mesh screen. Transfer granules to a twin-sell blender, add items 4 and 5, and blend for 6 to 8 minutes. Compress the granulation in a rotary press using 3/8-inch standard punches. Tablet weight is 260 mg.

Phenylpropanolamine, Chlorpheniramine, Dextromethorphan, Vitamin C Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
150.00	1	PEG-400 (low color), NF	150.00
21.66	2	Acetaminophen, USP	21.66
0.075 mL	3	Glycerin, USP (96%)	75.00 mL
0.35 mL	4	Sorbitol; use sorbitol solution, USP	350.00 mL
1.00	5	Benzoic acid, USP	1.00
1.75	6	Saccharin sodium (dihydrate powder), USP	1.75
0.91	7	Phenylpropanolamine hydrochloride, USP	916.70 mg
0.06	8	Chlorpheniramine maleate, USP (plus 10% manufacturing)	73.30 mg
0.66	9	Dextromethorphan hydrobromide, USP	667.00 mg
20.00	10	Sodium CMC (premium low viscosity)	20.00
70.00	11	Dye	70.00 mg
6.00	12	Dye	6.00 mg
5.00	13	Ascorbic acid; use sodium ascorbate (fine powder)	5.62
0.50	14	Flavor, orange	500.00 mg
0.25	15	Flavor, orange	250.00 mg
QS	16	Carbon dioxide gas	QS
QS	17	Purified water, USP	QS to 1 L

MANUFACTURING DIRECTIONS

Manufacture under complete CO₂ protection. Bubble the CO₂ gas through the solution from the bottom of the tank. If excessive foaming occurs, change CO₂ gas protection from the bottom to the top of the tank. Minimize vortex formation while mixing to prevent aeration of the product. In a covered stainless steel container, heat 500 mL of water to boiling. Boil for 30 minutes. Turn off the heat; while keeping the container covered, cool the water to 30°C while purging the water with CO₂. Keep this water in a covered container blanketed with CO₂ gas, and use where indicated. Transfer the PEG-400 to the main stainless steel mixing tank, and cover. Start bubbling CO₂ gas; while mixing, slowly heat to 60 to 65°C. Maintain at this temperature. While mixing, add and dissolve the acetaminophen. Maintain the temperature and CO₂ protection. When all the acetaminophen has dissolved, add, while mixing, the glycerine and sorbitol. Continue mixing while maintaining the temperature and CO₂ gas protection until mixture is used later. *Do not allow the temperature to go above 65°C.* During this mixing period, remove samples through the bottom valve of the mixing tank, and inspect for clarity; return samples to the mixing tank. Continue mixing and sampling until absolutely clear. In a separate stainless steel mixing tank, heat 300 mL of water, covered, to 90°C. While maintaining at this temperature, start bubbling CO₂ gas. While mixing, add and dissolve successively the benzoic acid, sac-

charin sodium, and phenylpropanolamine hydrobromide. Continue mixing until all have dissolved. Reduce the temperature to 60 to 65°C while mixing. *Do not force cool.* Add the solution from step above to the solution in the main mixing tank, while mixing and bubbling CO₂ gas. Rinse the container with 2 lots of 5 mL of CO₂-saturated water, and add the rinsings to the batch while mixing. Continue mixing for 15 minutes while maintaining the temperature at 60 to 65°C and under CO₂ gas protection. While mixing the batch, sprinkle on the sodium CMC. Continue mixing until all the sodium CMC has been dispersed. Check on the absence of any undissolved lumps. Add CO₂-saturated water from I.C. to 900 mL, and mix while cooling the batch to 30°C. Dissolve the dyes in 10 mL of CO₂-saturated water, then add to the batch with mixing. Rinse the container with 2 lots of 5 mL of the same water, and add the rinsings to the batch. Mix until a homogenously colored batch is formed. Stop bubbling in CO₂ gas but maintain CO₂ protection of the tank headspace. In a stainless steel container, dissolve the sodium ascorbate in 25 mL of CO₂-saturated water, taking care to minimize exposure of the solution to air or light. Mix all solutions, add rinsings where necessary, and continue mixing for 15 minutes. Add the flavors, complete the batch to 1 L with CO₂-saturated water, and mix well for 1 hour. Stop mixing, saturate the headspace with CO₂, and leave overnight to release any entrapped air.

Placebo Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
299.70	1	Ludipress®	299.70
0.30	2	Magnesium stearate	0.30

MANUFACTURING DIRECTIONS

Mix the components, sieve, and press. For this formulation, compress 300 mg. The compression force determines

hardness and friability. At 7 kN, the hardness is 45 N; at 22 kN, the hardness is 160 N. The disintegration time increases from 1 minute to 4 minutes.

Polidocanol Wound Spray

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
5.00	1	Polidocanol	5.00
50.00	2	Kollidon® VA 64	50.00
50.00	3	Ethocel® 20	50.00
20.00	4	Lutrol E 400	20.00
675.00	5	Ethyl acetate	675.00
200.00	6	Isopropanol	200.00

MANUFACTURING DIRECTIONS

Dissolve items 1 to 4 in the solvent mixture of items 5 and 6. Fill the solution into spray cans with the necessary

quantity of propellant (e.g., propane/butane) or in a mechanical pump bottle.

Polyvinylpyrrolidone–Iodine Mouthwash

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
100.00	1	Polyvinylpyrrolidone (PVP)–iodine	100.00
5.00	2	Saccharin sodium	5.00
2.00	3	Menthol	2.00
0.50	4	Aniseed oil	0.50
0.50	5	Eucalyptus oil	0.50
160.00	6	PEG-400	160.00
300.00	7	Ethanol	300.00
QS	8	Purified water	QS to 1 kg

MANUFACTURING DIRECTIONS

Dissolve PVP–iodine powder and saccharin sodium in 440 g of water to obtain a clear solution. In a separate container, add alcohol. Mix and dissolve aniseed oil, eucalyptus oil,

menthol, and PEG-400 to obtain a clear solution. QS with water. Add solution from step above and mix with stirring. Package in HDPE plastic bottles.

Povidone–Iodine and Lidocaine Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
100.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	100.00
10.00	2	Lidocaine hydrochloride	10.00
10.00	3	Sodium chloride	10.00
200.00	4	Lutrol F 127	200.00
79.00	5	Sodium hydroxide (1- <i>M</i> solution)	79.00
61.10	6	Water	61.10

MANUFACTURING DIRECTIONS

Dissolve items 1 to 3 in item 6, cool to about 6°C, dissolve item 4, and adjust the pH to a value of 4.5 to 5.0 with

item 5. Maintain the cool temperature until the air bubbles escape. Viscosity (Brookfield, 23°C) is 54,000 mPa.

Povidone–Iodine Bar Soap

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
50.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	50.00
10.00	2	Fragrance	10.00
75.00	3	Water	75.00
940.00	4	Syndet base	940.00

MANUFACTURING DIRECTIONS

Dissolve PVP–iodine in water, and mix the solution with the fragrance and the syndet base. Pass the blend four times through a three-roller mill. Blend three times through a plodder with a narrow sieve hole disk. Pass the blended material through a wide sieve hole disk combined

with a mouth hole disk. Heat the area of the two disks to 50°C using a heating collar. Cut the bar in pieces on a lab stamper. Composition of the syndet base (in sequence of concentration): disodium lauryl sulfosuccinate, sodium lauryl sulfate, cetylstearyl alcohol, paraffin, glycerol stearate, water, titanium dioxide.

Povidone–Iodine Bar Soap

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
50.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	50.00
75.00	2	Water	75.00
241.5	3	Texapon® K 12	241.5
241.5	4	Setacin® F special paste	241.5
241.5	5	Emcol® 4400.1	241.5
145.00	6	Cetylstearyl alcohol	145.00
96.50	7	Paraffin	96.50
226.00	8	Glycerol monostearate	226.00

MANUFACTURING DIRECTIONS

Heat mixture of items 3 to 8 to 75 to 80°C, and cool to about 50°C, stirring well. Add solution of items 1 and 2,

and let cool to room temperature, stirring continuously. Pass the blend four times through a three-roller mill and let dry overnight at room temperature. Cut the bar into pieces on a lab stamper.

Povidone–Iodine Bar Soap

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
50.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	50.00
75.00	2	Water	75.00
241.50	3	Texapon® K 12	241.50
145.00	6	Cetylstearyl alcohol	145.00
96.50	7	Paraffin	96.50
226.00	8	Glycerol monostearate	226.00

MANUFACTURING DIRECTIONS

Heat mixture of items 3 to 8 to 75 to 80°C, and cool to about 50°C, stirring well. Add solution of item 1, and let cool to room temperature, stirring continuously. Pass the

blend four times through a three-roller mill, and let dry overnight at room temperature. Cut the bar into pieces on a lab stamper.

Povidone–Iodine Concentrates for Broilers and Cattle

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
200.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	200.00
50.00	2	Texapon® K 12	50.00
50.00	3	Cremophor NP 14	50.00
73.00	4	Tartaric acid	73.00
43.00	5	Sulfuric acid, diluted	43.00
100.00	6	Ethanol 96%	100.00
QS	7	Water	QS to 1 kg

MANUFACTURING DIRECTIONS

Dissolve surfactant items 2 and 3 in solution of items 4 to 7, and slowly add PVP–iodine. Brown, transparent liquids

having a pH of about 1. Dilute about 3 mL of the concentrate with 1 L of water prior to use.

Povidone–Iodine Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
100.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	100.00
241.00	2	Citric acid (0.1- <i>M</i> solution)	241.00
369.00	3	Na ₂ HPO ₄ (0.2- <i>M</i> solution)	369.00
20.00	4	Cremophor A 6	20.00
20.00	5	Cremophor A 25	20.00
100.00	6	Cetylstearyl alcohol	100.00
100.00	7	Liquid paraffin	100.00
50.00	8	Glycerol	50.00

MANUFACTURING DIRECTIONS

Prepare a basic cream from the emulsifying agents and

the fatty substances (items 4 to 8). Stir in the PVP–iodine dissolved in the buffer solutions made from items 2 and 3. A brown cream having a pH of 4.5 is obtained.

Povidone–Iodine Effervescent Vaginal Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
350.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06, with excess	360.00
1450.00	2	Ludipress®	1450.00
360.00	3	Tartaric acid	360.00
265.00	4	Sodium bicarbonate	265.00
19.00	5	Talc	19.00
2.00	6	Calcium arachinate	2.00
2.00	7	Aerosil® 200	2.00

MANUFACTURING DIRECTIONS

Dry the mixture of items 2 to 4 for 4 hours at 60°C, mix with item 1 and items 5 to 7, and press to tablets. Compress

2.5 g in 20-mm biplanar punches. The tablet is dissolved in water to obtain a vaginal douche solution.

Povidone–Iodine Foam Spray

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
100.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	100.00
0.10	2	Cremophor A 25	0.10
QS	3	Water	QS to 1 kg

MANUFACTURING DIRECTIONS

Dissolve PVP–iodine in the solution of Cremophor A 25 in water. Fill the aerosol cans with 90 parts of this solution and 10 parts of propane + one part butane.

Povidone–Iodine Gargle

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
10.00	1	Polyvinylpyrrolidone-iodine (powder) (35% excess)	13.50
10.00	2	Glycerin, USP (96%)	10.00
—	3	Purified water, USP	QS to 1 L

MANUFACTURING DIRECTIONS

Wear gloves and mask during all phases of manufacturing and filling. Do not keep the lid of the manufacturing or storage tank open, unless necessary, as iodine may be liberated. Add 600 mL purified water to a suitable stainless steel manufacturing tank. Slowly add Povidone–iodine powder to the water (with continuous stirring). Stir for 30

minutes or until a clear, brown solution is obtained. Add glycerin to the manufacturing tank. Stir until uniform solution is obtained. Make up volume to 1.0 L with purified water, and mix well for 5 minutes. Check pH (range: 2.0 to 4.0). Filter the solution through a 100-mesh nylon cloth and transfer to a stainless steel storage tank. Keep the storage tank tightly closed.

Povidone–Iodine Gargle Solution Concentrate

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
100.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	100.00
10.00	2	Propylene glycol	10.00
90.00	3	Ethanol (96%)	90.00
800.00	4	Water	800.00

MANUFACTURING DIRECTIONS

Dissolve the PVP–iodine in the solvent mixture to produce a brown transparent liquid. Dilute 10 mL of the concentrate with about 100 mL of water prior to use.

Povidone–Iodine Gel-Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
100.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	100.00
359.00	2	Citric acid (0.1- <i>M</i> solution)	359.00
181.00	3	NA ₂ HPO ₄ · 12H ₂ O (0.2- <i>M</i> solution)	181.00
50.00	4	Lutrol E 400	50.00
100.00	5	Liquid paraffin	100.00
150.00	6	Lutrol F 127	150.00
70.00	7	Lutrol F 127	70.00

MANUFACTURING DIRECTIONS

Dissolve item 1 in solution of items 2 to 4, mix with item 5, and dissolve item 6 at about 20°C. Cool to 5 to 8°C,

and dissolve item 7. Maintain cool temperature until all air bubbles have disappeared. A brown, turbid gel is obtained.

Povidone–Iodine Gels

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
100.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	100.00
10.00	2	Sodium chloride	10.00
200.00	3	Lutrol F 127	200.00
79.00	4	Sodium hydroxide (1- <i>M</i> solution)	79.00
610.00	5	Water	610.00

MANUFACTURING DIRECTIONS

Dissolve items 1 and 2 in item 5, and cool to about 6°C. Dissolve Lutrol F 127 and item 2, and adjust the pH value

with item 4. Maintain cool until all air bubbles escape. Viscosity (Brookfield, 23°C) is 61,000 to 54,000 mPa; pH value (20% in water) is 2.2 to 4.6.

Povidone–Iodine Glucose Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
20.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06, with excess	26.00
45.00	2	Ethanol (96%)	45.00
849.00	3	Glucose	849.00
34.00	4	Lutrol E 4000	34.00
6.00	5	Glycerol	6.00
6.00	6	Water	6.00

MANUFACTURING DIRECTIONS

Dissolve Lutrol E 4000 in the hot mixture of glycerol and water, and add the glucose warmed to 60 to 80°C. Incorporate item 4 to obtain a brown, viscous, and turbid paste.

Povidone–Iodine Liquid Spray

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
100.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	100.00
150.00	2	Kollidon® VA 64	150.00
750.00	3	<i>n</i> -Propanol	750.00
750.00	4	Ethanol	750.00

MANUFACTURING DIRECTIONS

Dissolve Kollidon VA 64 in the mixture of solvents, and slowly add PVP–iodine to the well-stirred solution.

Fill in aerosol cans with propellants such as propane and butane or with manual valves.

Povidone–Iodine Lozenges

Bill of Materials			
Scale (mg/Lozenge)	Item	Material Name	Quantity/1000 Lozenges (g)
5.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	5.00
150.00	2	Sorbitol (crystallized)	150.00
4.00–5.00	3	Menthol (crystalline)	4.00–5.00
4.00–5.00	4	Eucalyptol (crystalline)	4.00–5.00
1.00	5	Aspartame, potassium	1.00
0.10	6	Saccharine sodium	0.10
1.00	7	Aerosil® 200	1.00
1.00	8	Magnesium stearate	1.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with medium compression force. Compress 176 mg in 8-mm biplanar punches.

Povidone–Iodine Mastitis Cream for Cattle

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
100.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	100.00
100.00	2	Liquid paraffin	100.00
100.00	3	Vaseline®	100.00
50–80	4	Cetylstearyl alcohol	50–80
20.00	5	Cremophor A 6	20.00
20.00	6	Cremophor A 25	20.00
50.00	7	Propylene glycol	50.00
QS	8	Water	530–560

MANUFACTURING DIRECTIONS

Dissolve PVP–iodine in the solvents (items 7 and 8). Mix items 2 to 6 by heating, stir the solution in the previous mixture, and cool by stirring.

Povidone–Iodine Mouthwash and Gargle Solution Concentrate

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
75.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	75.00
5.00	2	Saccharin sodium	5.00
150.00	3	Water	150.00
2.00	4	Menthol	2.00
1.00	5	Anise oil + eucalyptus oil (1+1)	1.00
150.00	6	Lutrol E 400	150.00
500.00	7	Ethanol (96%)	500.00

MANUFACTURING DIRECTIONS

Dissolve PVP–iodine and saccharin in water, and mix with solution of items 4 to 7. Brown transparent liquid has a

fresh odor. Dilute 10 to 20 mL with a glass of water. A brown liquid with a fresh tastes is obtained.

Povidone–Iodine Powder Spray

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
250.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	250.00
250.00	2	Maize PO ₄ aerosol	250.00
15.00	3	Isopropyl myristate	15.00
100.00	4	Dow Corning® 344 Fluid	100.00
500.00	5	Pentane	500.00
220.00	6	Propane + butane (1+3)	220.00

MANUFACTURING DIRECTIONS

Suspend PVP–iodine and maize PO₄ aerosol in the liquid

mixture of items 3 to 5, and fill in aerosol cans with the propellants.

Povidone–Iodine Pump Spray

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
10.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	10.00
100.00	2	Water	100.00
1.00	3	Potassium iodide	1.00
100.00	4	Xylitol	100.00
787.50	5	Propylene glycol	787.50
1.00	6	Menthol (crystalline)	1.00
0.50	7	Peppermint oil (double rectified)	0.50

MANUFACTURING DIRECTIONS

Dissolve potassium iodide in water, warm up to 40°C, and dissolve xylitol. At room temperature, dilute with

propylene glycol, dissolve PVP–iodine, and add flavors to produce a clear, brown liquid with a sweet, refreshing taste.

Povidone–Iodine Shampoo

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
75.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	75.00
250.00	2	Neutronyx® S 60	250.00
40.00	3	Super Amide® L 9	40.00
5.0–7.0	4	Natrosol® 250 HR	5.0–7.0
—	5	Water	QS to 1 kg

MANUFACTURING DIRECTIONS

Dissolve Super Amide and Natrosol in hot water (about 60°C), then dissolve PVP–iodine. After cooling, incorpo-

rate Neutronyx. A brown, clear solution is obtained. The viscosity can be changed by modification of the amount of Natrosol 250 HR.

Povidone–Iodine Soft Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
10.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	10.00
25.00	2	Natrosol® HR 250	25.00
QS	3	Water	QS to 1 kg

MANUFACTURING DIRECTIONS

Dissolve PVP–iodine and Natrosol HR 250 in the water, and stir well to produce a clear, brown gel. Viscosity (Brookfield, 23°C) is 31,500 mPa.

Povidone–Iodine Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
100.00	1	Povidone–iodine powder (35% excess)	135.00
9.318	2	Anhydrous citric acid (powder)	9.318
14.62	3	Anhydrous sodium phosphate (dibasic)	14.62
QS	4	Purified water	QS to 1 L

MANUFACTURING DIRECTIONS

Wear gloves and mask during all phases of manufacturing and filling. Do not keep the lid of the manufacturing or storage tank open, unless necessary, as iodine may be liberated. *Citric acid-phosphate buffer solution (pH 5.0)*: Add 600 mL purified water to a suitable stainless steel manufacturing tank. With gentle stirring add citric acid to the purified water in the manufacturing tank. Stir for 10 minutes or until completely dissolved. During this mixing period, remove samples from the bottom valve of the manufacturing tank, and inspect for clarity. Return samples to the manufacturing tank. Continue mixing and sampling until the solution is completely clear. With gentle stirring add dibasic sodium phosphate to the solution. Stir for 10 minutes or until completely dissolved. During this mixing period, remove samples from the bottom valve of the manufacturing tank, and inspect for clarity. Return

samples to the manufacturing tank. Continue mixing and sampling until the solution is completely clear. Make up volume to 1 L with purified water, and mix well for 5 minutes. Check and record pH (range: 4.8 to 5.2). Filter the solution through a 100-mesh nylon cloth. Transfer into a suitable stainless steel storage tank, and keep tightly closed. This solution should be freshly prepared and should not be stored for more than 24 hours. *Preparation of solution*: Dissolve povidone–iodine in about 600 mL of citric acid/phosphate buffer (pH 5.0) solution in a suitable stainless steel mixing tank. Stir evenly for 10 minutes or until a clear brown solution is obtained. Make up volume to 1 L with citric acid/phosphate buffer solution. Mix well for 10 minutes. Check and record pH (range: 3.0 to 4.5). Filter the solution through a 100-mesh nylon cloth. Transfer into a suitable stainless steel storage tank, and keep it tightly closed.

Povidone–Iodine Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
100.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	100.00
3.00	2	Lutrol F 127	3.00
5.00	3	Lutrol E 400	5.00
432.00	4	Citric acid (0.1- <i>M</i> solution)	432.00
460.00	5	Na ₂ HPO ₄ · 12H ₂ O (0.2- <i>M</i> solution)	460.00

MANUFACTURING DIRECTIONS

Dissolve the PVP–iodine (and Lutrol F 127) in the mixture of buffer solutions (and Lutrol E 400). Brown clear solutions

having a low viscosity and pH of about 4.5. Items 2 and 3 can be deleted and compensated with item 5.

Povidone–Iodine Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
100.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	100.00
0.23	2	Texapon® K 12	0.23
1.40	3	Sodium biphosphate	1.40
0.30	4	Sodium citrate	0.30
20.80	5	Sodium hydroxyde (1- <i>M</i> solution)	20.80
10.00	6	Glycerol	10.00
QS	7	Water	QS to 1 kg

MANUFACTURING DIRECTIONS

Dissolve Texapon K 12 in solution of items 3 to 7, and slowly add PVP–iodine to the well-stirred solution. The brown, transparent liquid has a pH of 4.5.

Povidone–Iodine Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
100.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	100.00
10.00	2	Natrosol® HR 250	10.00
2.00	3	Lutrol F 127	2.00
32.00	4	Sodium hydroxide (1- <i>M</i> solution)	32.00
QS	5	Water	QS to 1 kg

MANUFACTURING DIRECTIONS

Dissolve Lutrol F 127 and then Natrosol in the water. As soon as both are dissolved, slowly add the PVP–iodine to the well-stirred solution. Adjust the pH with the sodium hydroxide solution to about 3.5.

Povidone–Iodine Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
20.00	1	Tylose® M 300	20.00
2.00	2	Texapon® K 12	2.00
595.00	3	Citric acid (0.1- <i>M</i> solution)	595.00
283.00	4	Sodium biphosphate (0.2- <i>M</i> solution)	283.00

MANUFACTURING DIRECTIONS

Dissolve Tylose M 300 in the mixture of the citric acid and sodium biphosphate solutions. Add Texapon, and slowly dissolve the PVP–iodine. The brown, clear solution has a pH of 3 to 4.

Povidone–Iodine Scrub

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
75.00	1	Polyvinylpyrrolidone-iodine (powder) (40% excess)	105.00
250.00	2	Sodium lauryl sulfate	250.00
35.00	3	Lauric diethanolamide	35.00
—	4	Distilled purified water, USP	QS to 1 L

MANUFACTURING DIRECTIONS

Add 600 mL purified water to a suitable stainless steel manufacturing tank. Add, by sprinkling, the sodium lauryl sulfate to the manufacturing tank. Continue to mix slowly under vacuum, and begin to heat until product temperature is 70°C. Continue to mix vigorously under vacuum at 65 to 70°C for 15 minutes, or until completely dissolved. (*Note:* Do not add detergent quickly, as a gel may form that is difficult to dissolve.) Stop mixer, release vacuum, and open tank. Add and disperse the previously broken lauric diethanolamide in the warmed solution from the step above. Maintain vacuum, and mix vigorously for 30 minutes at 65 to 70°C or until completely dissolved. Slowly cool under vacuum to room temperature with slow mixing. (*Note:* Do not force cool with cold water; other-

wise, the mixture will adhere to the walls of the manufacturing tank.) When temperature reaches 30°C, release vacuum and open tank. While mixing slowly, add Povidone–iodine in small portions. Rinse the container of Povidone–iodine with 150 mL purified water, and add to the main tank. (*Note:* Do not keep the lid of the manufacturing or storage tank open, unless necessary, as iodine may liberate.) Mix under vacuum until a clear reddish brown solution is obtained. Make volume up to 1.0 L with purified water, and mix well under vacuum for at least 15 minutes to ensure product uniformity and to deaerate the product. Stop mixing, release the vacuum, then open the tank. Check and record pH (range: 3.0 to 6.0). Filter the solution through 100-mesh nylon cloth.

Povidone–Iodine Surgical Scrub

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
75.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	75.00
250.00	2	Neutronyx® S 60	250.00
40.00	3	Super Amide® L 9	40.00
QS	4	Floral bouquet	QS
QS	5	Water	QS to 1 kg

MANUFACTURING DIRECTIONS

Dissolve Super Amide in hot water, cool, dissolve PVP–iodine and add Neutronyx to produce a brown, clear viscous solution with pH of about 3.4.

Povidone–Iodine Surgical Scrub

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
75.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	75.00
250.00	2	Lutensit® AES	250.00
40.00	3	Monoamide® 150 MAW	40.00
QS	4	Floral bouquet	QS
QS	5	Water	QS to 1 kg

MANUFACTURING DIRECTIONS

Dissolve Monoamide in hot water, cool, dissolve PVP–iodine, and add Lutensit to produce a brown, clear, viscous solution.

Povidone–Iodine Transparent Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
100.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	100.00
600.00	2	Lutrol E 400	600.00
46.00	3	Sodium hydroxide (1- <i>M</i> solution)	46.00
4.00	4	Water	4.00
250.00	5	Lutrol E 4000	250.00

MANUFACTURING DIRECTIONS

Prepare solution of items 1 to 4, heat to about 60°C, incorporate item 6 (stirring very well), and cool to room temperature. The transparent ointment, similar to a gel, has a pH of 4 and is miscible and washable with water.

Povidone–Iodine Vaginal Douche Concentrate

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
100.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	100.00
5.00	2	Lutrol E 400	5.00
3.00	3	Lutrol F 127	3.00
432.00	4	Citric acid (0.1- <i>M</i> solution)	432.00
460.00	5	Na ₂ HPO ₄ · 12H ₂ O (0.2- <i>M</i> solution)	460.00

MANUFACTURING DIRECTIONS

Dissolve PVP–iodine and Lutrol F 127 in the mixture of buffer solutions with Lutrol E 400. The brown, clear solution has a low viscosity and pH of about 4.3.

Povidone–Iodine Vaginal Ovule

Bill of Materials			
Scale (mg/Ovule)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	5.00
200.00	2	Lutrol E 400	10.00
170.00	3	Lutrol E 4000	85.00

MANUFACTURING DIRECTIONS

Melt the Lutrol E grades by gentle heating. Stir in the micronized PVP–iodine product in small portions into the

melt. After a uniform suspension has been obtained, pour it into polyethylene molds. The homogeneous, brown-colored ovule has a weight of 2.0 g.

Povidone–Iodine Vaginal Ovule

Bill of Materials			
Scale (mg/Ovule)	Item	Material Name	Quantity/kg (g)
200.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	200.00
100.00	2	Lutrol E 400	100.00
100.00	3	Lutrol E 1500	100.00
700.00	4	Lutrol E 4000	700.00

MANUFACTURING DIRECTIONS

Melt the Lutrol E grades by gentle heating. Stir in the micronized PVP–iodine product in small portions into the

melt. After a uniform suspension has been obtained, pour it into polyethylene molds. The homogeneous, brown-colored ovule has a weight of 2.0 g.

Povidone–Iodine Viscous Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
10.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	10.00
15.00	2	Natrosol® HR 250	15.00
QS	3	Buffer	QS
QS	4	Water	975.00

MANUFACTURING DIRECTIONS

Dissolve PVP–iodine and Natrosol in the well-stirred buffered solution in water to produce a clear, brown, viscous liquid. Viscosity (Brookfield) is 7500 mPa.

Promethazine Hydrochloride Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
1.00	1	Promethazine HCl (5% exces)	1.05
675.00	2	Sucrose	675.00
1.00	3	Citric acid (monohydrate)	1.00
2.40	4	Sodium citrate	2.40
0.50	5	Ascorbic acid	0.50
0.25	6	Sodium metabisulfite (sodium disulfite)	0.25
0.25	7	Anhydrous sodium sulfite	0.25
50.00	8	Alcohol (ethanol, 95%)	50.00
0.15	9	Flavor	0.15
0.30	10	Flavor	0.30
0.50	11	Polysorbate 80 (Tween 80)	0.50
0.15	12	Caramel color	0.15
QS	13	Purified water	QS to 1 L

MANUFACTURING DIRECTIONS

Promethazine HCl undergoes thermal and photochemical oxidation. Protect from light, heat, and oxygen as practicable. Avoid vortex or over-mixing to avoid air entrapment. Use nitrogen gas whenever necessary to expel air. Add 400.0 g of item 13 to the manufacturing vessel, and heat to 90 to 95°C. Add item 2 while mixing at slow speed. After addition of item 2, mix for 30 minutes at high speed and a temperature of 90 to 95°C. Cool down to 30 to 35°C while mixing at low speed. Add items 3 and 4 to the manufacturing vessel while mixing, and mix until dissolved. Add items 6 and 7 to the manufacturing vessel while mixing, and mix until dissolved. Add item 5 to the manufacturing vessel while mixing, and mix until dissolved. Mix items 9 and 10 with items 8 and 11 in a separate container by using stirrer. Mix for 10 minutes, and add to the manufacturing vessel while mixing. Add 8.0 g of cold purified water (25 to 30°C) to a separate

container, and dissolve item 12 by using stirrer. Mix for 10 minutes, and add to the manufacturing vessel while mixing. Start flushing the syrup with nitrogen gas pressure at 20 to 40 psi. Add 10.0 g of cold purified water (cooled and flushed with N₂ gas) in a separate container with lid. Pass nitrogen gas at 20 to 40 psi pressure for 15 minutes. Dissolve item 1 in nitrogen-flushed, cold purified water (25 to 30°C) by using stirrer. Mix for 10 minutes, and add to the manufacturing vessel while mixing. Do not produce vortex. Bring volume up to 1 L with nitrogen-flushed purified water. Continue flushing nitrogen gas at 20 to 40 psi pressure for 30 minutes while mixing at slow speed. Check and record the pH (limit: 4.5 to 5.5). If required, adjust pH with 10% citric acid or 10% sodium citrate solution. Filter the syrup at 1.5 bar. Recirculate about 20 to 30 mL syrup. Transfer the filtered syrup to the storage vessel. Flush with nitrogen gas, and seal the tank.

Promethazine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Promethazine HCl	10.50
41.95	2	Lactose monohydrate	41.95
20.00	3	Maize starch	20.00
0.05	4	Sodium metabisulfite (sodium disulfite)	0.05
2.00	5	Povidone (PVP K-30)	2.00
5.00	6	Maize starch (dried)	5.00
0.50	7	Magnesium stearate	0.50
—	8	Alcohol (ethanol, 95%)	6.07
—	9	Purified water	8.67

MANUFACTURING DIRECTIONS

Avoid over-mixing of lubricants; otherwise, hardness will be reduced. Mix items 9 and 8 in a stainless steel container. Dissolve items 4 and 5 by slow stirring with stirrer until mixture becomes clear. Sift items 1, 2, and 3 through a stainless steel 500- μ m sieve in sifter. Load into mixer, and mix for 5 minutes at low speed. Add binding solution at a rate of 5 to 7 g/minute to the dry powders, while mixing at low speed. After addition is complete, scrape sides and blades. Mix further for 2 minutes using a mixer and chopper at low speed. Scrape sides and blades. Check for the end point of granulation, which is the point where the granulation consists of few or no lumps. If required, add purified water. Dry the wet granules with the air circulation heater off to expel alcohol for 2 hours. Then, dry at

55°C for 14.0 hours. After 4.0 hours of drying, scrape the semidried granules to break up the lumps to promote uniform drying. Check the LOD (limit: 1.0 to 1.5%). If required, dry further at 55°C for 2 hours. Grind the dried granules through a 1.25-mm sieve using a granulator at medium speed. Collect in stainless steel drums. Load granules into the blender. Sift item 6 material through a 500- μ m sieve using a sifter, and add it into blender. Mix for 3 minutes. Sift item 7 through a 500- μ m sieve, and add 1 to 2 g of granules from above. Mix in polyethylene bag for 1 minute. Add to blender. Mix for 30 seconds. Compress 0.80 g. Coat using one of the HPMC coatings in the Appendix.

For 25 mg tablets, use the following formula:

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Promethazine HCl	26.00
103.75	2	Lactose monohydrate	103.75
50.00	3	Maize starch	52.50
1.50	4	Sodium metabisulfite (sodium disulfite)	1.50
5.00	5	Povidone (PVP K-30)	5.00
12.50	6	Maize starch (dried)	12.50
1.25	7	Magnesium stearate	1.25
—	8	Alcohol (ethanol, 95%)	15.00
—	9	Purified water	21.67

Pseudoephedrine Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Quantity/1000 Capsules (g)
24.00	1	Pseudoephedrine hydrochloride	24.00
15.00	2	Hydroxyethylcellulose, NF	15.00
60.00	3	Anhydrous lactose	60.00
1.00	4	Magnesium stearate	1.00

MANUFACTURING DIRECTIONS

Blend all the ingredients in a twin-shell blender for 10 minutes. Fill No. 0 capsules with fill weight of 500 mg using a tamping force of 200 N.

Pseudoephedrine Hydrochloride Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
6.00	1	Pseudoephedrine HCl (3.0% excess)	6.18
600.00	2	Sucrose	600.00
100.00	3	Glycerin (glycerol)	100.00
100.00	4	Sorbitol (70% solution)	100.00
15.00	5	Propylene glycol	15.00
1.00	6	Methyl paraben	1.00
0.30	7	Propyl paraben	0.30
0.50	8	Saccharin sodium	0.50
0.02	9	Dye (if needed)	0.02
0.05	10	Menthol	0.05
0.13	11	Citric acid	0.13
1.15	12	Sodium citrate	1.15
QS	13	Purified water	QS to 1 L

MANUFACTURING DIRECTIONS

Add 390.0 g of purified water to the manufacturing vessel, and heat to 90 to 95°C. Add items 6 and 7 while mixing to dissolve at high speed. Add item 2 while mixing at slow speed at a temperature of 90 to 95°C. Mix for 1 hour at high speed. Cool down to 50°C while mixing at slow speed. Dissolve items 8 and 12 in 10.0 g of item 13, and add to the manufacturing vessel while mixing at high speed. Dissolve item 11 in 10.0 g of purified water, and add to the manufacturing vessel while mixing at high speed. Load items 4 and 3 into the manufacturing vessel using a transfer pump while mixing at high speed. Mix for 5 minutes. Cool down to 30°C while mixing at slow

speed. Add 20.0 g of item 13 (30°C) in a separate container, and dissolve item 1 by using stirrer. Mix for 10 minutes, and add to the manufacturing vessel while mixing at high speed. Add 6.0 g of item 13 in a separate container, and dissolve item 9 manually. Add color to the manufacturing vessel while mixing at high speed. Dissolve item 10 in item 5. Add this flavor mixture to the manufacturing vessel while mixing at high speed. Bring the volume up to 1 L with item 13, and finally mix for 15 to 20 minutes at high speed. Check and record the pH (limit 5.5 to 6.5 at 25°C). If required, adjust pH with 20% citric acid or 20% sodium citrate solution. Filter the syrup at 1.5 bar. Recirculate about 100 to 150 mL syrup.

Pseudoephedrine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
60.00	1	Pseudoephedrine HCl ^a	63.00
120.20	2	Lactose monohydrate	120.20
25.00	3	Maize starch	25.00
1.00	4	Povidone (PVP K-30)	1.00
4.00	5	Povidone (PVP K-30)	4.00
1.80	6	Magnesium stearate	1.80
—	7	Alcohol (ethanol, 95%)	29.00

^a Pseudoephedrine HCl 3.0 mg/tab can be added in excess to compensate for moisture and handling loss.

MANUFACTURING DIRECTIONS

Avoid over-mixing of lubricants; otherwise, hardness is reduced. Dissolve item 5 in item 7 while mixing at slow speed using a stirrer. Sift items 1, 2, 3, and 4 through a 500- μ m sieve. Load into mixer, and mix for 5 minutes at low speed. Add binding solution to the dry powders while mixing at low speed for 2 minutes. After addition is complete, mix further for 1 minute using mixer and chopper at low speed. Scrape sides and blade. Check for the end point of granulation, which is when the granulation consists of wet granules with few or no lumps. If required, add ethanol 95% to achieve desired granules. Record extra

quantity of ethanol 95% used. Dry the wet mass at 55°C for 7.0 hours. After 4 hours of drying, scrape the semidried granules to break the lumps to promote uniform drying. Check the moisture content (limit: 1.5 to 2.5%). Sift the dried granules through a 1.25-mm sieve using a granulator at medium speed. Collect in stainless steel drums. Load granules into the drum blender. Sift item 6 through a stainless steel 250- μ m sieve in sifter. Add 8 to 12 g granules in mixer to sieved item 6. Mix manually for 1 minute. Add to drum blender, and blend for 1 minute. Compress 215 mg in 8-mm round punches.

Pseudoephedrine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
60.00	1	(+) Pseudoephedrine hydrochloride	60.00
95.00	2	Dicalcium phosphate (Di-Tab)	95.00
5.00	3	Kollidon® 30	5.00
—	4	Water	QS
20.00	5	PEG-6000 (powder)	20.00
2.00	6	Aerosil® 200	2.00

MANUFACTURING DIRECTIONS

Granulate dicalcium phosphate with solution of items 3 and 4, dry, pass through an 0.8-mm sieve, and mix with

item 1. Add items 5 and 6, and press with low compression force. Compress 192 mg using 8-mm biplanar punches.

Pseudoephedrine Hydrochloride, Carbinoxamine Maleate Oral Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
500.00	1	Sucrose	500.00
300.00	2	Glucose liquid	300.00
150.00	3	Glycerine (96%)	150.00
30.00	4	<i>d</i> -Pseudoephedrine hydrochloride	30.00
1.00	5	Carbinoxamine maleate	1.00
4.00	6	Saccharin sodium (powder)	4.00
2.50	7	Sodium benzoate (powder)	2.50
1.25	8	Flavor	1.25
0.03	9	Dye	0.03
0.03	10	Dye	0.03
QS	11	Hydrochloric acid reagent-grade bottles	QS
QS	12	HyFlo filter aid	1.32
QS	13	Purified water	455.00
QS	14	Sodium hydroxide for pH adjustment	QS

MANUFACTURING DIRECTIONS

Charge 315 mL of deionized water into a suitable tank. Begin heating water to 60 to 70°C while adding sucrose with stirring. Stir until sugar is dissolved. Remove heat. Add glucose liquid and 125 g of glycerin in this step. Add and dissolve *d*-pseudoephedrine HCl, carbinoxamine maleate, saccharin sodium, and sodium benzoate with mixing. Cool solution to 30 to 35°C. Mix flavor with 25 g of glycerin. (*Note:* Temperature of syrup must not be

higher than 35°C.) Dissolve dyes, if used, in 5 mL of deionized water, and add to syrup with mixing. Adjust to pH 4.25 (range: 4.0 to 4.5), if necessary, with hydrochloric acid or sodium hydroxide. QS to 1 L with deionized water, and mix well. Allow product to stand overnight to let entrapped air escape. Readjust volume to 1 L with deionized water. Add and mix 1.320 g of HyFlo filter aid to the product. Circulate through a press. Filter into tank for filling.

Psoriasis Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
40.00	1	Lanolin alcohol	40.00
50.00	2	White petroleum jelly	50.00
120.00	3	Paraffin wax 140F	120.00
300.00	4	Mineral oil (70 cS)	300.00
20.00	5	Coal tar	20.00
2.50	6	Allantoin	2.50
QS	7	Deionized water	QS to 1 kg
QS	8	Preservative	QS

MANUFACTURING DIRECTIONS

Heat oil and water phases separately to 70°C. Slowly add water phase in increments to the oil phase. Allow each

addition time to be fully incorporated. Stir to cool. Fill just above melting point. Further homogenization may improve stability prior to filling.

Psoriasis Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
160.00	1	Stearic acid	16.00
60.00	2	Oleyl alcohol	6.00
20.00	3	Lanolin	2.00
20.00	4	Coal tar	2.00
6.00	5	Triethanolamine (99%)	0.60
2.50	6	Allantoin	0.25
QS	7	Deionized water	QS to 1 kg
—	8	Preservative	QS

MANUFACTURING DIRECTIONS

Heat water and oil phases separately to 80°C. Add water phase to oil phase while stirring. Stir to cool. Pass through homogenizer. Fill at 40°C.

Pyridoxine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
40.00	1	Pyridoxine hydrochloride	40.00
150.00	2	Lactose monohydrate	150.00
150.00	3	Avicel™ PH101	150.00
15.00	4	Kollidon® VA 64*	15.00
10.00	5	Kollidon® CL*	10.00
1.00	6	Magnesium stearate	1.00
1.00	7	Aerosil® 200	1.00

MANUFACTURING DIRECTIONS

Pass all components through a 0.5-mm sieve, mix, and press with high compression force. Compress 361 mg in 12-mm biplanar punches; items marked with asterisk can be deleted when the compression weight becomes 340 mg.

Pyridoxine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
40.00	1	Pyridoxine hydrochloride	40.00
300.00	2	Corn starch	300.00
15.00	3	Kollidon® 30	15.00
80.00	4	Water + isopropanol	80.00
1.00	5	Magnesium stearate	1.00
2.00	6	Aerosil® 200	2.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 and 2 with solution of items

3 and 4, dry, pass through an 0.8-mm sieve, mix with items 5 and 6, and press with high compression force. Compress 354 mg in 12-mm biplanar punches.

Pyridoxine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Pyridoxine hydrochloride	100.00
200.00	2	Tabletlose®	200.00
10.00	3	Kollidon® VA 64	10.00
3.00	4	Kollidon® CL	3.00
1.00	5	Magnesium stearate	1.00
1.00	6	Aerosil® 200	1.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with medium compression force. Compress 363 mg in 12-mm biplanar punches.

Pyridoxine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Pyridoxine hydrochloride	100.00
150.00	2	Lactose monohydrate	150.00
83.00	3	Avicel™ PH101	83.00
10.00	4	Kollidon® VA 64	10.00
3.00	5	Kollidon® CL	3.00
1.00	6	Magnesium stearate	1.00
1.00	7	Aerosil® 200	1.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix and press with medium compression force. Compress 360 mg in 12 mm-biplanar punches.

Pyridoxine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Pyridoxine hydrochloride	250.00
100.00	2	Avicel™ PH101	100.00
12.00	3	Kollidon® VA 64	12.00
5.00	4	Magnesium stearate	5.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with high compression force. Compress 361 mg in 12-mm biplanar punches.

Pyridoxine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Pyridoxine hydrochloride	300.00
100.00	2	Lactose monohydrate D 20	100.00
20.00	3	Kollidon® 30	20.00
QS	4	Isopropanol + water (1+1)	60.00
10.00	5	Kollidon® CL	10.00
2.00	6	Aerosil® 200	2.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 and 2 with solution of items 3 to 6, dry, and sieve through an 0.8-mm screen. Press

with medium compression force. Compress 440 mg using 12-mm biplanar punches.

Ranitidine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
75.00	1	Ranitidine; use Ranitidine HCl ^a	85.00
95.00	2	Microcrystalline cellulose (Avicel™ PH102)	95.00
7.00	3	Croscarmellose sodium (Ac-Di-Sol)	7.00
6.60	4	Microcrystalline cellulose (Avicel™ PH102)	6.60
1.40	5	Magnesium stearate	1.40

^a Ranitidine HCl (1.5%) is added to compensate LOD and process loss.

MANUFACTURING DIRECTIONS

Process the product in an area where the relative humidity is 40 to 45% and temperature does not exceed 25°C. Store the bulk tablets in polyethylene-lined stainless steel containers at a controlled relative humidity of 45 to 50% and temperature not exceeding 25°C. Pass items 2, 3, and 1 through a sifter using a 900-µm sieve. Load into a blender, and mix for 3 minutes. Manually mix items 4 and 5 in a polyethylene bag for 1 minute. Pass through a sifter using a 500-µm sieve. Collect in a polyethylene bag. Add to

blender, and blend for 1 minute. Check temperature and humidity before start of slugging (at a temperature not exceeding 25°C and a relative humidity of 40 to 45%). Slug 240.0 g of mixed powder in a rotary tableting machine. Grind the slugs in a granulator using a 3.0-mm sieve followed by a 1.00-mm sieve. Compress 195 mg using oblong biconvex punches. Check temperature and humidity before start of compression (limit: temperature not exceeding 25°C and relative humidity of 40 to 45%). Coat using a hydroalcoholic HPMC coating.

Ranitidine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
75.00	1	Ranitidine; use Ranitidine HCl	88.88
65.00	2	Microcrystalline cellulose, NF	65.00
1.12	3	Magnesium stearate, NF	1.12

MANUFACTURING DIRECTIONS

Pass Ranitidine and microcrystalline cellulose through a 595- μ m screen, and transfer to a suitable mixer. Mix for 10 minutes. Screen the magnesium stearate through a 400- μ m screen and add to the blender. Blend for 2 minutes. Com-

press using slightly convex round punches at hardness 8 ppi and disintegration time of not more than 15 minutes in water. Coat using a methocel-ethocel coating solution (see Appendix).

Riboflavin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
3.00	1	Riboflavin	3.00
195.00	2	Ludipress®	195.00
2.00	3	Magnesium stearate	2.00
1.00	4	Aerosil® 200	1.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with very low compression force (4 kN). Compress 202 mg using 8-mm biplanar punches. This is a very low active ingredient formulation (3 mg). If content uniformity

is a problem, prepare a premix of the active ingredient with a small part of the Ludipress® or with lactose monohydrate before mixing with the other components of the formulation.

Riboflavin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Riboflavin	10.00
75.00	2	Lactose monohydrate	75.00
20.00	3	Corn starch	20.00
15.00	4	Avicel™ PH101	15.00
5.00	5	Kollidon® 30	5.00
25.00	6	Water	25.00
0.80	7	Aerosil® 200	0.80
2.50	8	Talc	2.50
1.70	9	Hydrogenated castor oil	1.70

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 4 with solution of items 5 and 6, dry, pass through an 0.8-mm sieve, mix with items

7 to 9, and press with low compressive force. Compress 134 mg in 8-mm biplanar punches.

Riboflavin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
75.00	1	Riboflavin	75.00
375.00	2	Sorbitol (crystalline)	375.00
23.00	3	Kollidon® VA 64	23.00
4.00	4	Magnesium stearate	4.00
12.00	5	Aerosil® 200	12.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with low compressive force. Compress 493 mg using 12-mm biplanar punches.

Riboflavin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Riboflavin	100.00
250.00	2	Sorbitol (crystalline)	250.00
19.00	3	Kollidon® VA 64	19.00
5.00	4	Magnesium stearate	5.00
10.00	5	Aerosil® 200	10.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with medium compression force. Compress 384 mg using 12-mm biplanar punches.

Riboflavin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
150.00	1	Riboflavin, with excess	156.00
150.00	2	Ludipress®	150.00
4.00	3	Magnesium stearate	4.00
2.00	4	Aerosil® 200	2.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with low compressive force. Compress 308 mg using 8-mm biplanar punches.

Rubefacient Analgesic Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
150.00	1	Polawax, NF	150.00
100.00	2	Methyl salicylate	100.00
50.00	3	Menthol	50.00
100.00	4	Mineral oil (70 cS)	100.00
QS	5	Deionized water	QS to 1 kg
QS	6	Preservative, color	QS

MANUFACTURING DIRECTIONS

Heat oil and water phases separately to 70°C. Add water phase to oil phase while stirring; stir to cool. Fill at 30°C.

Saccharin Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
15.00	1	Saccharin sodium	15.00
10.00	2	Tartaric acid	10.00
14.00	3	Sodium bicarbonate	14.00
2.00	4	Kollidon® VA 64	2.00
2.00	5	PEG-6000 (powder)	2.00

MANUFACTURING DIRECTIONS

Dry saccharin sodium and tartaric acid 1 hour at 100°C. Mix all components, pass through an 0.8-mm sieve, and

press with low compressive force. Compress 42 mg in 5-mm biplanar punches.

Saccharin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
37.50	1	Sodium cyclamate	37.50
17.00	2	Mannitol	17.00
6.35	3	Soda ash (light-milled powder, 58% Na ₂ O)	6.35
3.75	4	Saccharin sodium (dihydrated powder)	3.75
1.40	5	Povidone (PVP K-29–32)	1.40
8.00	6	Purified water	8.00
11.00	7	Tartaric acid	11.00
0.80	8	Soda ash (light-milled powder, 58% Na ₂ O)	0.80
1.00	9	Anhydrous sodium citrate	1.00
1.00	10	Sodium benzoate	1.00
0.20	11	PEG-8000	0.20

MANUFACTURING DIRECTIONS

This product is hygroscopic and should be processed in a low-humidity area not exceeding 50% relative humidity at 24°C. Maintain at 35 to 40% relative humidity at 24°C if possible. If necessary, pass sodium cyclamate and mannitol (if used) through a Fitz mill or similar type using a 420-μm or similar screen, then charge into a suitable mixer. To this mixture, add soda ash (item 3), and blend for 30 minutes or until uniform. Dissolve Povidone in 4 mL of warm purified water. Dissolve saccharin sodium in 3 mL of warm purified water. Add solutions from previous steps together plus sufficient purified water. Mass with blended powders. Blend for 1 hour or until uniform. Pass the wet mass through a 4.76-mm or similar screen in an oscillating granulator, and

spread onto trays. Oven dry at 50 to 55°C for 16 to 24 hours using a full oven load of trays (LOD NMT 0.9%). Pass dried granulation through a 1.19-mm or similar screen in an oscillating granulator or through a 1.68-mm or similar screen using a comminuting mill (knives forward, slow speed). Lubricants must meet LOD/moisture content before proceeding. If lubricants fail, dry them at 80°C for 8 hours. Use 60°C for tartaric acid. Mill lubricants (except tartaric acid and granulated lactose, if used) through a 600-μm or similar screen in a comminuting mill (hammers forward, medium speed). Load dried granulation, coated tartaric acid, lactose (if used), and milled lubricants into a suitable mixer and blend for 30 to 40 minutes. Compress 80 mg per tablet in 7/32-inch punches.

Saccharin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
15.00	1	Saccharin sodium	15.00
31.00	2	Ludipress®	31.00
2.00	3	Kollidon® CL	2.00
0.30	4	Magnesium stearate	0.30
2.00	5	PEG-6000 (powder)	2.00
2.00	6	Lutrol F 68	2.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with medium compression force. Compress 51 mg

(or 50 mg if items 5 and 6 are omitted) using 5-mm punches.

Salicylic Acid Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
150.00	1	Glyceryl stearate and PEG-75 stearate	150.00
5.00	2	Stearic acid	5.00
80.00	3	Mineral oil	80.00
665.00	4	Deionized water	665.00
100.00	5	Salicylic acid	100.00

MANUFACTURING DIRECTIONS

Mix and heat items 1 to 4 to 75°C. Allow to cool with gentle stirring. At 30°C, add item 5; homogenize if necessary.

Selegiline Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Selegiline	5.00
94.00	2	Ludipress®	94.00
1.00	3	Magnesium stearate	1.00

MANUFACTURING DIRECTIONS

Mix all components intensively, pass through an 0.8-mm sieve, and press with low compressive force. Compress 99 mg in 6-mm biplanar punches.

Selenium Sulfide Shampoo with Conditioner

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
10.00	1	Selenium sulfide	10.00
2.00	2	Methyl paraben	2.00
10.00	3	Magnesium aluminum silicate type IIA	10.00
20.00	4	Titanium	20.00
0.17	5	Dye	0.17
230.00	6	Sodium alkyl ether sulfate/sulfonate	230.00
30.00	7	Cocamide DEA surfactant	30.00
40.00	8	Cocoamphocarboxyglycinate	40.00
10.00	9	Hydrolyzed protein	10.00
4.00	10	Perfume	4.00
QS	11	Citric acid	QS
QS	12	Sodium chloride	QS
QS	13	Deionized purified water	QS to 1 L

Note: Item 11 is used for pH adjustment, if necessary, and item 12 is used for viscosity adjustment, if necessary.

MANUFACTURING DIRECTIONS

Selenium sulfide is toxic; handle carefully, and use approved respiratory protection. Add 7 mL of purified water to an appropriate mill containing full-charge alumina grinding cylinder media. Add selenium sulfide. Seal the mill, and agitate for approximately 10 minutes to wet down the powdered material. Recycle for approximately 5 minutes with the pump set at 1040 mmHg. Stop agitation. If necessary, add purified water (25 to 30°C) to nearly cover the grinding media. Seal the mill, and recirculate the slurry for 1–2 hours with the pump set to obtain the required particle size specifications for the selenium sulfide. Load 250 mL of purified water into a suitable jacketed mixing tank and heat to 60 to 70°C. With good stirring, add and dissolve methyl paraben. Slowly add and disperse the magnesium aluminum silicate. Continue mixing until fairly smooth. Stop mixing, and allow to hydrate for 1 hour. Add and disperse titanium dioxide. Mix for 30

minutes. With good stirring, add the selenium sulfide slurry, and rinse the mill with purified water. Mix for 30 minutes. Stop mixing and add sodium lauryl ether sulfate/sulfonate. Mix slowly for 5 minutes. Add cocamide DEA. Mix slowly for approximately 3 minutes. Add cocoamphocarboxyglycinate. Mix slowly for 30 minutes. Separately dissolve hydrolyzed protein (hydrogel) in 4 mL of purified water, and mix until uniform. Add solution from above to the tank, and mix until uniform. Add perfume, and mix for 1 minute. Dissolve dye in 2 mL of warm purified water (50 to 60°C), and add to mixing tank. Mix until uniform. Check and record pH; adjust to 4.5 to 5.0, if necessary, using citric acid. Record amount of citric acid used and the adjusted pH. Add purified water QS to 980 mL, and mix for 30 minutes. Check and record viscosity. If necessary, adjust by adding sodium chloride. Deaerate by slow stirring under vacuum or use of a suitable deaerator. Mix for 1 hour.

Serratia Peptidase Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Serratia peptidase	10.00
228.00	2	Ludipress®	228.00
2.00	3	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix intensively, and press with low compressive force (6 kN). Compress 238 mg in 8-mm biplanar punches.

Silicone Protective Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
150.00	1	Polawax, NF	150.00
40.00	2	Oleyl alcohol	40.00
50.00	3	PEG-75 lanolin	50.00
150.00	4	Mineral oil (70 cS)	150.00
50.00–100.00	5	Dimethicone	50.00–100.00
QS	6	Deionized water	QS to 1 kg

MANUFACTURING DIRECTIONS

Heat water and oil phase separately to 60 to 65°C. Add the water phase to the oil phase while stirring. Stir to cool to 30°C. May add perfume or color as desired.

Silimarin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
35.50	1	Silimarin	35.50
410.50	2	Ludipress®	410.50
4.50	3	Magnesium stearate	4.50

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with low compressive force (about 10 kN). Compress 458 mg in 12-mm biplanar punches.

Simethicone Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
70.00	1	Simethicone dry powder 25%	280.00
158.00	2	Sucrose, powder	158.00
7.00	3	Kollidon® 90 F	7.00
3.50	4	Kollidon® 90 F	3.50
QS	5	Isopropanol	QS
2.80	6	Aerosil® 200	2.80

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 3 with solution of items 4 and 5, dry, pass through an 0.8-mm sieve, add item 6, mix thoroughly, and press with high compressive force. Compress 442 mg in 12-mm biplanar punches.

Simethicone Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
80.00	1	Simethicone (Wacker silicon oil, S184)	80.00
400.00	2	Sorbitol, (crystalline)	400.00
20.00	3	Aerosil® 200	20.00
390.00	4	Ludipress®	390.00
2.00	5	Menthol (powder)	2.00
8.00	6	Magnesium stearate	8.00

MANUFACTURING DIRECTIONS

Mix items 2 and 3 with item 1, pass through an 0.8-mm sieve, add mixture of items 4 to 6, mix thoroughly, pass

again through an 0.8-mm sieve, and press with high compressive force. Compress 870 mg using 16-mm biplanar punches.

Simethicone Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
70.00	1	Simethicone	70.00
71.40	2	Microcrystalline cellulose	71.40
71.40	3	Magnesium hydroxide	71.40
265.00	4	Mannitol	265.00
100.00	5	Lactose	100.00
395.10	6	Granular sugar	395.10
0.70	7	Menthol	0.70
10.00	8	Fumed silica	10.00
5.00	9	Fumed silica	5.00
10.00	10	Magnesium stearate	10.00

MANUFACTURING DIRECTIONS

Blend item 2 and item 3 in a V-blender for 10 minutes. Transfer to planetary mixer. Slowly add weighted amount of item 1 to the mix, and mix slowly using a “B” flat

beater blade; after thorough mixing, pass through a #20-mesh screen. Add the balance of the ingredients, mix, and compress.

Sodium Fluoride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
0.50	1	Sodium fluoride	0.55
56.25	2	Sorbitol, crystalline	56.25
56.25	3	Dicalcium phosphate	56.25
2.20	4	Kollidon® VA 64	2.20
0.50	5	Magnesium stearate	0.50

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with high compressive force. Compress 116 mg using 6-mm biplanar punches. If the content uniformity

is not sufficient, a premix of sodium fluoride and sorbitol or dicalcium phosphate should be prepared separately before mixing with the rest of the excipients.

Sodium Fluoride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1.30	1	Sodium fluoride	1.30
76.70	2	Ludipress®	76.70
0.40	3	Magnesium stearate	0.40

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with low compressive force. Compress 78 mg using 5-mm biplanar punches. If the content uniformity does

not meet the requirements, prepare a premix of the active ingredient with a small part of the Ludipress® or with lactose monohydrate before mixing with the other components of the formulation.

Spirulina Extract Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Spirulina extract (powder)	250.00
245.00	2	Ludipress®	245.00
25.00	3	PEG-6000 (powder)	25.00
5.00	4	Aerosil® 200	5.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with medium compressive force. Compress 495 mg using 12-mm biplanar punches.

Sucralfate and Sodium Alginate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Sucralfate	500.00
20.00	2	Sodium alginate	20.00
70.00	3	Corn starch	70.00
20.00	4	Kollidon® 30	20.00
—	5	Ethanol (95%)	80.00 mL
30.00	6	Kollidon® CL	30.00
3.00	7	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 3 with solution of items 4 and 5, pass through a sieve, mix the dry granules with items 6 and 7, and press with low compressive force. Compress 660 mg using 12-mm biplanar punches.

Sulfur Antiseptic Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/1000 Tablets (g)
15.00	1	Sulfur (precipitated)	15.00
85.00	2	Kaolin	85.00
QS	3	White petroleum jelly	QS to 1 kg
60.00	4	Isopropyl palmitate	60.00
13.00	5	Camphor	13.00
13.00	6	Methyl salicylate	13.00
20.00	7	Lanolin	20.00
50.00	8	Tribehenin	50.00
50.00	9	Ozokerite	50.00
35.00	10	Sorbitan oleate	35.00
15.00	11	Deionized water	15.00
4.00	12	Salicylic acid	4.00
24.00	13	Glycerin	24.00
QS	14	Preservative	QS

MANUFACTURING DIRECTIONS

Heat oils, except sulfur and lanolin, to 70°C. Disperse sulfur and kaolin in the oil phase. Heat water, glycerin, and salicylic acid gently. Add to oil phase while stirring. Stir to 55°C. Mill to disperse sulfur.

Tannin–Crospovidone Complex Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
55.00	1	Tannic acid	55.00
230.00	2	Water	230.00
230.00	3	Kollidon® CL	230.00
33.00	4	Avicel™ PH101	33.00
2.60	5	Talc	2.60
0.30	6	Aerosil® 200	0.30
0.30	7	Calcium arachinate	0.30

MANUFACTURING DIRECTIONS

Prepare solution of items 1 and 2, suspend item 3, and filter the formed insoluble tannin–crospovidone complex. Wash with water until the water is clear, pass the solids

through an 0.8-mm sieve, and dry. Add items 4 to 7, and press with low compressive force. Compress 323 mg using 12-mm biplanar punches.

Tetrahydrozoline Eye Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
17.20	1	Acid boric	17.20
1.50	2	Hydroxypropyl methylcellulose 2910 (4000 cps)	1.50
0.40	3	Borax	0.40
1.00	4	Disodium edetate	1.00
0.50	5	Tetrahydrozoline hydrochloride	0.50
0.00063 mL	6	Benzalkonium chloride solution (17%)	0.63 mL
QS	7	Water purified	QS to 1 L

MANUFACTURING DIRECTIONS

Use thoroughly cleaned and rinsed steam-jacketed, glass-lined tank or stainless steel tank (#304 or better), equipped with a speed-controlled agitator; the tank should have a cover. Foaming occurs due to the benzalkonium chloride, which concentrates in the foam; processing and filling systems should be designed to minimize foaming and allow rapid dissipation of foaming. Charge 80% of the final volume of water into the mixing tank. If using methylcellulose, heat deionized water to 90°C. While agitating, add and disperse methylcellulose by slowly sprinkling it on the surface of solution; mix to avoid excessive foaming. Allow 15 minutes for hydration of the methylcellulose before discontinuing heating, and allow to cool to 40°C. While agitating, add and dissolve disodium edetate, benzalkonium chloride, boric acid, sodium borate, and tetrahydrozoline; continue cooling

to 25°C. Discontinue agitation and QS to 1 L with deionized water. (*Note:* Methylcellulose solutions filter at a slow rate.) Use inline Pall and Sartorius cartridges, and recirculate solution until clear; transfer to holding or sterilization. Use either heat sterilization or sterile filtration. *Heat sterilization:* Sterilize at 112 to 115°C for 60 minutes, cool solution to 25 to 30°C, and aseptically add the sterile tetrahydrozoline solution; mix well. Set up a previously sterilized filter and transfer line with 10-µm stainless steel FulFlo filter or equivalent. Aseptically fill sterile solution into sterilized containers, and apply sterile closure components. *Sterile filtration:* Use Pall cartridge with Sartorius Cartridge; prepare and steam-sterilize the recommended filter units. Aseptically fill the sterilize solution into each sterilized container, and apply sterile closure.

Thiamine and Caffeine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Thiamine hydrochloride	500.00
100.00	2	Caffeine	100.00
30.00	3	Corn starch	30.00
20.00	4	Kollidon® VA 64	20.00
15.00	5	Kollidon® VA 64	15.00
QS	6	Ethanol (96%)	QS
35.00	7	PEG-6000 (powder)	35.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 4 with solution of item 5 and 6, dry, sieve, mix with item 7, and press with low compressive force. Compress 698 mg using 16-mm biplanar punches.

Thiamine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Thiamine HCl with excess	110.00
43.50	2	Lactose monohydrate	43.50
4.00	3	Crospovidone (Kollidon® CL)	4.00
5.50	4	Povidone (PVP K-90)	5.50
5.50	5	Crospovidone (Kollidon® CL)	5.50
32.00	6	Microcrystalline cellulose (Avicel™ PH112)	32.00
5.60	7	Talc (fine powder)	5.60
3.70	8	Glyceryl behenate (glyceryl monostearate)	3.70
0.20	9	Magnesium stearate	0.20
—	10	Alcohol (ethanol, 95%)	50.67

MANUFACTURING DIRECTIONS

Sift items 1, 2, and 3 through a stainless steel 630-µm sieve. Load into mixer. Mix for 5 minutes at high speed. Dissolve item 4 in item 10 under slow stirring by stirrer. Add the binding solution while mixing at high speed over a period of 2 minutes. Scrape sides and blades. Mix and chop at high speed for 2 minutes. Check the end point of granulation. If required, add additional item 10 to obtain the end point. (The end point of granulation occurs when the wet mass consists of few or no lumps.) Dry wet granules in oven at 55°C for 8.0 hours. After 2.0 hours of drying, scrape the semidried granules to break up the lumps to promote uniform drying. Check the LOD (limit:

1.0 to 1.5%). If required, dry at 55°C for an additional hour. Check the LOD. Grind the dried granules through a 1.25-mm sieve with the granulator set at medium speed. Collect in stainless steel drums. Load the granules into blender. Sift items 5 and 6 through a 500-µm sieve, and add to blender. Mix for 2 minutes (do not overmix). Sift items 8 and 9 through a 500-µm sieve. Add 1.33 to 2.67 g of granules. Mix in a polyethylene bag for 1 minute. Add to blender. Blend for 1 minute. Check temperature and humidity before start of compression (limit: temperature should not exceed 25°C; relative humidity, 45 to 50%). Compress using 8-mm, round, beveled, concave punches.

Thiamine Hydrochloride Tablets, Sugar-Coated

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Thiamine hydrochloride monohydrate (with excess)	110.00
110.00	2	Lactose	110.00
5.00	3	Luviskol® K-98	5.00
1.00	4	Magnesium stearate	1.00
40.00	5	Ethyl alcohol (denatured)	40.00
251.44	6	Sugar (crystalline)	251.44
1.40	7	Sugar powder	1.40
14.50	8	Maize starch	14.50
14.81	9	Talcum	14.81
21.00	10	Copolymer lacquer	21.00
0.40	11	Paraffin (solid)	0.40
0.16	12	Gum acacia	0.16
0.228	13	Ethyl alcohol (denatured)	0.228
0.01	14	Paraffin (liquid)	0.01
QS	15	Purified water	QS

MANUFACTURING DIRECTIONS

In a suitable stainless steel vessel, add denatured ethyl alcohol and Luviskol; mix until homogeneous mixture is obtained. Set aside. Pass lactose through a #2-mesh sieve, add thiamine, and mix for 10 minutes in an appropriate mixer. Slowly add to this mixture the solution made earlier, and stir until slightly lumpy mass is obtained. If required, add ethyl alcohol to the mixture. Pass the wet mass through an oscillating granulator with a 7.00-mm perforated sieve. Spread the granules over paper-lined trays, and dry at 40°C for 5 hours in a drying oven. The relative humidity of the granules should be 15 to 25%. Pass magnesium stearate and talcum through a 1-mm hand sieve. Compress on a rotary tablet machine at about 4 to 5 tons of pressure; the weight of each tablet should be about 230 mg. In a suitable container, add purified water and acacia gum; pass the resulting solution through an 0.8-mm sieve. Charge the compressed tablets into a coating pan and apply the copolymer lacquer in ten portions; after the last application, apply neutral spray (crystalline sugar in demineralized water). Dry the insulated tablets in a drying oven overnight at 45°C (minimum 14 hours); the tablet weight should be around 236 mg each. In an electric, jacketed kettle, put demineralized water, crystalline sugar, maize starch, and talcum; mix by stirring until homogeneous. Pass through a sieve of mesh size 0.8 mm (pH, 6.0 to 8.0; density, 1.335 to 1.356). Coat the tablets to 400 mg weight using the coating solution and a sugar-coating pan; set pans at slow speed, open air inlets, and set air inflow at 80°C and maximum contact temperature set at 42°C. Roll tablets to reach this temperature. Turn pan to fast speed, close the inlet air flap, and make first application of syrup. When all tablets are wet and distri-

bution of syrup is uniform, open the air inlet flap and allow 80°C air to blow (tablet temperature falls 1 to 2°C for a short time and then slowly rises to 42°C). The next application of the syrup cycle begins. Coat the tablets with color solution as described above to 495-mg weight. Set the air inflow temperature at 25°C, and reduce the size of application with the falling temperature, whereby tablets are evenly and lightly moistened after each application; the temperature drops from 42 to 32°C. Turn the coating pans slowly during the drying phase; for the last three applications, keep the pan lids closed, as well as the air intake and outflow during this phase. Drying only with outlet air may be extended for the last three applications up to 10 to 15 minutes. Immediately after the last application of syrup has dried slightly, begin the polishing step. The polishing paste is prepared in a suitable boiling vessel by adding stock gum solution, crystalline sugar, and demineralized water. Boil until temperature reaches 106°C with stirring. In a steam kettle, melt solid and liquid paraffin, and pour melted paraffins into the mixture of gum; make up the weight with demineralized water. Polishing paste ready for use contains 0.75 kg of paste and 0.113 kg of ethyl alcohol. Tablet temperature is 28 to 32°C. Shut off the inlet flaps and outlet flaps, set the pans at the fast speed, and add polishing paste (about 0.3% of tablet weight). Close the pans with inner lids and allow them to rotate at fast speed for 90 seconds for even distribution. Remove the inner lid of the pan, and set it on slow speed. Open the outlet air for 3 minutes, blow the inlet air at 40°C for 6 to 8 minutes until a good sheen appears. Set the pans on automatic system for overnight, with intermission time of 5 minutes off and 10 seconds on.

Thiamine, Pyridoxine, and Cyanocobalamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
110.00	1	Thiamine mononitrate	110.00
210.00	2	Pyridoxine hydrochloride	210.00
76.82	3	Lactose monohydrate	76.82
10.00	4	Crospovidone (Kollidon® CL)	10.00
18.50	5	Povidone (PVP K-90)	18.50
0.30	6	Cyanocobalamin	0.30
85.00	7	Microcrystalline cellulose (Avicel™ PH102)	85.00
14.00	8	Crospovidone (Kollidon® CL)	14.00
10.00	9	Glyceryl behenate (glyceryl monostearate)	10.00
0.49	10	Magnesium stearate	0.49
15.00	11	Talc (fine powder)	15.00
—	12	Alcohol (ethanol, 95%)	88.90

MANUFACTURING DIRECTIONS

Dissolve item 5 in item 12 by using a stirrer to make a clear solution. Dissolve item 6 carefully in the solution. Sift items 1 to 4 through a 630- μ m sieve. Load the material into a mixer. Mix and chop at high speed for 5 minutes. Add binding solution from previous step to the dry powder in the mixer while mixing and chopping at high speed for 2 minutes. Check for satisfactory wet mass. Add additional item 12, if required, to obtain a satisfactory wet mass. Do not allow big lumps. Record the additional quantity of ethanol 95%. Spread the granules onto stainless steel trays to a thickness of 1/4th of the tray thickness, and load the trays onto a trolley. Load the trolley into an oven. Keep the door open, switch on the oven with air circulation,

heater turned off for 2 hours. Dry the granules at 55°C for 12 hours. Check the LOD of dried granules (limit: NMT 0.7%). Grind the dried granules through a 1.25-mm sieve using a granulator. Collect in a stainless steel drum. Load into the blender. Sift items 7, 8, and 9 through a 500- μ m sieve. Collect in stainless steel container. Load the sieved powder into the blender. Blend for 3 minutes. Sift items 11 and 10 through a 500- μ m sieve. Collect in a polyethylene bag. Add 4.44 to 6.67 g of granules from earlier step, and mix manually for 1 minute. Add this mixture to the blender, and mix for 1 minute. Compress the granules using a rotary tableting machine. Compress 550 mg using round, binconvex punches at 9 to 16 kp. Coat tablets using an HPMC coating (see Appendix).

Thiamine, Pyridoxine, and Cyanocobalamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Thiamine mononitrate (powder)	115.00
50.00	2	Pyridoxine hydrochloride	50.00
9.75	3	Anhydrous Citric Acid (powder)	9.75
20.10	4	Monohydrate lactose (powder, regular)	20.10
1.67	5	Saccharin sodium	1.67
0.24	6	Dye	0.24
0.009	7	Dye	0.009
0.02	8	Dye	0.02
2.00	9	Corn Starch	2.00
QS	10	Purified water	18.00 mL
50.00 µg	11	Vitamin B12; use vitamin B12 oral powder cobalamin conc	62.50
12.50	13	Monohydrate lactose (powder, regular)	12.50
1.50	14	Oil orange terpeneless	1.50
3.50	15	Magnesium stearate	3.50
1.50	16	Talc (powder)	1.50
17.70	17	Corn starch, Light Coral Red 6 LA	17.70

MANUFACTURING DIRECTIONS

Pass thiamine mononitrate, pyridoxine HCl, citric acid, lactose (item 4), and saccharin sodium through a #30-mesh (595-µm or similar) screen. Charge into mixer, and dry mix. Dissolve the dyes in purified water. Add the starch (item 9) to this dye solution with stirring. Heat and continue stirring until a thick paste is formed. Cool to room temperature before using. (*Note:* Use 7.5 g of colored starch paste for the vitamin B1 and B6 blend and 12.5 g of colored starch paste for the vitamin B12 blend.) Add 7.5 g of colored starch paste to powder blend, and mix until mass is formed. Pass through a #6-mesh (3.36-mm or similar) screen, and air dry for 3 to 4 hours. Screen vitamin B12 oral powder and lactose (item 12) through a #30-mesh (595-µm or similar) screen. Charge into mixer, and dry mix. Add 12.5 g

colored starch paste to powder blend, and mix until mass is formed. Pass through #6-mesh (3.36-mm or similar) screen, and air dry for 3 to 4 hours. Dry granulations from the two steps separately at 49°C overnight or until LOD is less than 1%. Mill the two dried granulations through a #16-mesh (1.2-mm or similar) screen (knives forward, medium speed), and combine. Sift a small quantity of granulation from the steps above over a #30-mesh (595-µm or similar) screen, and add the orange oil to the fines. Add magnesium stearate, talc powder, and Light Coral Red starch to mixture, and pass through a #30-mesh (595-µm or similar) screen. Charge base granulation and lubricants into a blender, and blend thoroughly. Compress using 11/32-inch, concave punches.

Thiamine, Pyridoxine, and Cyanocobalamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Thiamine hydrochloride	100.00
10.00	2	Pyridoxine hydrochloride	10.00
0.10	3	Cyanocobalamin (gelatin-coated, 1%)	10.00
277.00	4	Ludipress®	277.00
3.00	5	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with low compressive force. Compress 394 mg in 12-mm biplanar punches.

Thiamine, Pyridoxine, and Cyanocobalamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Thiamine mononitrate	100.00
200.00	2	Pyridoxine hydrochloride	200.00
0.10	3	Cyanocobalamin (gelatin-coated, 1%)	10.00
250.00	4	Ludipress®	250.00
45.00	5	PEG-6000 (powder)	45.00
5.00	6	Aerosil® 200	5.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with low compressive force. Compress 609 mg using 12-mm biplanar punches.

Thiamine, Pyridoxine, and Cyanocobalamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Thiamine mononitrate	250.00
250.00	2	Pyridoxine hydrochloride	250.00
75.00	3	Lactose monohydrate	75.00
25.00	4	Kollidon® 30	25.00
QS	5	Isopropanol	QS
1.00	6	Cyanocobalamin (gelatin-coated, 1%)	100.00
25.00	7	Kollidon® CL	25.00
2.00	8	Magnesium stearate	2.00
2.00	9	Talc	5.00

MANUFACTURING DIRECTIONS

Granulate mixture items 1 to 3 with solution of items 4 and 5, dry, pass through an 0.8-mm sieve, mix with items

6 to 9, and press with low compressive force, applying a vibrating hopper. Compress 730 mg using 12-mm biplanar punches.

Thiamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Thiamine hydrochloride or thiamine mononitrate	50.00
293.00	2	Ludipress®	293.00
5.00	3	Magnesium stearate	5.00
2.00	4	Aerosil® 200	2.00

MANUFACTURING DIRECTIONS

Pass all components through a 0.5-mm sieve, mix, and press with medium compressive force. Compress 357 mg,

if hydrochloride salt is used, or 347 mg, if mononitrate salt is used, with 12-mm biplanar punches.

Thiamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Thiamine hydrochloride or thiamine mononitrate	50.00
150.00	2	Lactose monohydrate	150.00
150.00	3	Avicel™ PH101	150.00
15.00	4	Kollidon® CL	15.00
2.00	5	Aerosil® 200	2.00

MANUFACTURING DIRECTIONS

Pass all components through a 0.5-mm sieve, mix, and press with high compressive force. Compress 344 mg, if

hydrochloride salt is used, or 373 mg, if mononitrate salt is used, with 12-mm biplanar punches.

Thiamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Thiamine hydrochloride or thiamine mononitrate	110.00 (or 100.00)
190.00	2	Ludipress®	190.00
100.00	3	Lactose monohydrate	100.00
100.00	4	Avicel™ PH 101	100.00
9.00	5	Kollidon® CL	9.00
3.00	6	Aerosil® 200	3.00
2.00	7	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

Pass all components through a 0.5-mm sieve, mix, and press with medium compressive force. Compress 302 mg,

if hydrochloride salt is used, or 320 mg, if mononitrate salt is used, with 8-mm biplanar punches.

Thiamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Thiamine hydrochloride	100.00
200.00	2	Lactose monohydrate	200.00
10.00	3	Kollidon® 30	10.00
60.00	4	Isopropanol	60.00
10.00	5	Kollidon® CL	10.00
2.00	6	Magnesium stearate	2.00
1.00	7	Aerosil® 200	1.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 and 2 with solution of items 3 and 4, dry, and sieve through an 0.8-mm screen, mix

with items 5 to 7, and press to tablets. Compress 330 mg using 8-mm biplanar punches.

Thiamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Thiamine mononitrate	300.00
100.00	2	Dicalcium phosphate (Di-Tab)	100.00
15.00	3	Kollidon® 30	15.00
QS	4	Isopropanol	~50.00
10.00	5	Kollidon® CL	10.00
4.00	6	Magnesium stearate	4.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 and 2 with solution of items 2 and 3, dry, and sieve through an 0.8-mm screen. Mix with items 5 and 6, and compress 430 mg into tablets using 12-mm biplanar punches.

Tolnafate and Undecylanate Foot Care Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
150.00	1	Glyceryl stearate and PEG-75 stearate	150.00
20.00	2	Hydrogenated palm/palm kernel oil PEG-6 esters	20.00
60.00	3	Mineral oil	60.00
0.50	4	Sorbic acid	0.50
0.50	5	Sodium methylaraben	0.50
509.00	6	Deionized water	509.00
50.00	7	Undecylenic acid	50.00
200.00	8	Zinc undecylanate	200.00
10.00	9	Tolnafate	10.00

MANUFACTURING DIRECTIONS

Mix and heat items 1 to 7 to 75°C. Allow to cool with gentle stirring. At 30°C, add items 8 and 9. Homogenize, if necessary.

Tolnafate Foot Care Microemulsion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
155.00	1	Ethoxydiglycol	155.00
130.00	2	Polyglyceryl-6 dioleate	130.00
450.00	3	PEG-8 caprylic/capric glycerides	450.00
10.00	4	Tolnafate	10.00
100.00	5	Deionized water	100.00
50.00	6	Apricol kernel oil PEG-6 esters	50.00
100.00	7	Caprylic/capric triglycerides	100.00
5.00	8	Chlorocresol	5.00

MANUFACTURING DIRECTIONS

Mix items 1 to 3, and dissolve item 4 in this mixture. Add items 5 to 8, and mix until uniform.

Tolu Balsam Cough Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
11.03	1	Tolu balsam tincture	11.03
2.50	2	Magnesium carbonate (powder)	2.50
15.00	3	Sucrose (granulated sugar)	15.00
QS	4	Purified water	90.00 mL
0.77	5	Methyl paraben	0.77
0.086	6	Propyl paraben	0.86
514.36	7	Sucrose (granulated sugar)	514.36
129.24	8	Glycerin (96%)	129.24
2.00	9	Dextromethorphan hydrobromide	2.00
1.00	10	Ephedrine HCl (powder)	1.00
8.00	11	Ammonium chloride	8.00
0.40	12	Chlorpheniramine maleate	0.40
1.00	13	Phenylephrine HCl	1.00
333.32	14	Glucose (liquid)	333.32
0.35	15	Flavor	0.35
0.15	16	Flavor	0.15
1.01	17	Ipecac (fluid extract)	1.01
8.57	18	Alcohol (ethanol, 190 proof)	8.57
0.037	19	Dye	0.037
QS	20	Hydrochloric acid (reagent-grade bottles)	QS
QS	21	Purified water	212.00 mL

MANUFACTURING DIRECTIONS

Charge tolu balsam tincture into mixing tank, and add magnesium carbonate. Mix well to suspend. Add sugar (item 3) with mixing. Add 90 mL purified water (item 4), and mix thoroughly. Allow to set for 1 hour. Mix periodically while circulating through Shriver filter (or equivalent). Solution must be brilliantly clear. Filter and save for next part. Charge 210.5 mL purified water (item 21) into suitable tank. Add and dissolve parabens with heat (90 to 95°C) and mixing. Add and dissolve sugar (item 7) with mixing; heat if necessary. Add glycerine, continue agitation, and cool to room temperature. To cooled syrup, add filtrate from step above. Add and dissolve the following ingredients with mixing: dextromethorphan hydrobro-

mide, ephedrine HCl, ammonium chloride, chlorpheniramine maleate, and phenylephrine HCl. Add glucose. Mix well. Add and dissolve flavors and Ipecac fluid extract in 190-proof alcohol. To the tank *or* in a separate container add flavors and Ipecac extract to 10 mL of glucose liquid, and mix. Add this mixture to the main mixture. Rinse the container with a further 5 mL of liquid glucose, and add the rinsing to the mixture. Add the remaining liquid glucose. Mix well. Dissolve in 1.75 mL purified water, and add. Check pH (range: 4.0 to 5.0). Use hydrochloric acid to adjust pH to 4.0 to 5.0, with 4.5 being optimum (~0.3 mL HCl per liter of syrup). QS to 1 L with purified water. Filter until sparkling clear. Add a suitable filter aid and mix until uniform. Filter into tank for filling.

Triclosan and Zinc Foot Deodorant Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/1000 Tablets (g)
3.00	1	Triclosan (Irgasan® DP300)	3.00
2.00	2	Zinc undecylenate, USP	2.00
0.20	3	Menthol (crystals), USP	0.20
926.80	4	Talc (powder), USP	926.80
30.00	5	Magnesium stearate	30.00
30.00	6	Corn starch, NF	30.00
8.00	7	Perfume	8.00

MANUFACTURING DIRECTIONS

Pass the following ingredients through a 250- μ m screen or similar: Irgasan DP300, zinc undecylenate, magnesium stearate, corn starch, menthol, and approximately 10% of the total amount of talc. Charge materials from first step into a suitable mixer. Mix until uniform. Discharge pow-

der from second step into another suitable mixer. Add and disperse perfume. Mix until uniform. Pass mixture from step above through a 250- μ m screen or similar. Charge mixture from step above into a V-mixer or similar, and add balance of talc powder. Mix for 30 minutes or until homogeneous.

Triclosan Foot Care Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
50.00	1	Glyceryl stearate (gelol)	50.00
50.00	2	Propylene glycol stearate	50.00
100.00	3	Octyldodecyl myristate	100.00
50.00	4	Isostearyl isostearate	50.00
20.00	5	Dimethicone (100 cS)	20.00
651.00	6	Deionized water	651.00
50.00	7	Sucrose distearate	50.00
4.00	8	Phenoxyethanol, methyl paraben, ethyl paraben, and propyl paraben	4.00
20.00	9	Propyleneglycol	20.00
3.00	10	Triclosan	3.00
2.00	11	Fragrance	2.00

MANUFACTURING DIRECTIONS

Heat items 1 to 5 and items 6 to 7 separately to 75°C; mix the two parts with turbine mixing for 1 minute. Cool with

gentle stirring. Add items 9 and 10 and then item 11 with mixing at 30 to 35°C.

Triprolidine and Pseudoephedrine Hydrochloride Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
0.25	1	Triprolidine HCl (4.8% excess)	0.26
6.00	2	Pseudoephedrine HCl (3.0% excess)	6.18
600.00	3	Sucrose	600.00
100.00	4	Glycerin (glycerol)	100.00
100.00	5	Sorbitol (70% solution)	100.00
15.00	6	Propylene glycol	15.00
1.00	7	Methyl paraben	1.00
0.30	8	Propyl paraben	0.30
0.50	9	Saccharin sodium	0.50
0.04	10	Quinoline yellow	0.04
0.05	11	Menthol	0.05
0.25	12	Raspberry flavor	0.25
1.15	13	Sodium citrate	1.15
QS	14	Purified water	QS to 1 L

MANUFACTURING DIRECTIONS

Add 400.0 g of purified water to the manufacturing vessel, and heat to 90 to 95°C. Add items 7 and 8 while mixing to dissolve at high speed. Add item 3 while mixing at slow speed (temperature, 90 to 95°C). Mix for 1 hour at high speed. Cool down to 50°C while mixing at slow speed. Add items 9 and 13 to the manufacturing vessel while mixing at high speed. Load items 5 and 4 into the manufacturing vessel using a transfer pump while mixing at high speed. Add 20.0 g of cold purified water (30°C) in a separate container, and dissolve items 1 and 2 by using stirrer. Mix for 10 minutes, and add to the manufacturing

vessel while mixing at high speed. Add 1.0 g of purified water in a separate container, and manually dissolve item 10. Add color to the manufacturing vessel while mixing at high speed. Dissolve item 11 in item 12, then add item 6. Add this flavor mixture to the manufacturing vessel while mixing at high speed. Bring the volume up to 1.0 L with item 14, and finally mix for 15 to 20 minutes at high speed. Check and record the pH (limit: 5.8 to 6.8 at 25°C). If required, adjust pH with 20% citric acid or 20% sodium citrate solution. Filter the syrup at 1.5 bar. Recirculate about 20 to 30 mL syrup.

Triprolidine and Pseudoephedrine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.60	1	Triprolidine HCl (4% excess)	2.70
60.00	2	Pseudoephedrine HCl (5% excess)	63.00
122.40	3	Lactose monohydrate	122.40
25.50	4	Maize starch	28.00
1.00	5	Povidone (PVP K-30)	1.00
4.00	6	Povidone (PVP K-30)	4.00
—	7	Alcohol (ethanol, 95%)	28.00
1.50	8	Magnesium stearate	1.50

MANUFACTURING DIRECTIONS

Dissolve item 6 in item 7 using a stirrer. Avoid loss of ethanol by evaporation. Pass items 1 to 5 through a 630- μ m sieve using sifter. Collect in a stainless steel drum. Load the sieved powders into a mixer. Mix and chop for 5 minutes at low speed. Add PVP solution to the mixer at medium rate while mixing. Start the chopper at low speed when half of the solution is added. Mix and chop at low speed until the satisfactory mass is obtained. Spread the wet granules onto the trays. Keep the trolleys in the open air for about 1 hour. Load the trolleys into the oven, and start the air circulation at room temperature for 2 hours.

Dry the granules at 55°C with air circulation for 5 hours. Scoop the granules after 2 hours of drying; move the upper trays down and the lower trays up for uniform drying. Check the moisture content (limit: NMT 1.5%). Pass the dried granules through a 1-mm sieve using a granulator. Collect in a stainless steel drum and load into the blender. Pass item 8 through a 250- μ m sieve using a sifter. Collect in a polyethylene bag. Mix 2 g of granules with this mixture, and add to the blender. Mix for 1 minute. Unload the lubricated granules in a stainless steel drum. Compress 220 mg in 8.5-mm, round, concave punches.

Trolamine Salicylate Cream

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/kg (g)
50.00	1	Glyceryl stearate	5.00
25.00	2	Cetyl alcohol	2.50
30.00	3	Cetyl phosphate and DEA cetyl phosphate	3.00
40.00	4	Stearyl stearoyl stearate	4.00
40.00	5	Coco-caprylate/caprates	4.00
40.00	6	Cetyl palmitate	4.00
5.00	7	Dimethicone	0.50
502.00	8	Deionized water	50.20
10.00	9	Propylene glycol, diazolidinyl urea, methyl paraben, and propyl paraben	1.00
5.50	10	Magnesium aluminum silicate	0.55
2.50	11	Xanthan gum	0.25
100.00	12	Deionized water	10.00
100.00	13	Trolamine salicylate (TEA salicylate)	10.00
50.00	14	Propylene glycol	5.00

MANUFACTURING DIRECTIONS

Heat items 8 and 9 to 85°C, and add items 10 and 11. Mix until well dispersed. Add items 1 to 7, and mix well at 80

to 85°C. Continue mixing; while cooling to 65°C, add items 12 to 14, and continue mixing and cooling to 35°C. The pH should be 5.5 to 5.6.

Ultrasonic Adhesive Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
5.00	1	Preservative (e.g., parabenes)	5.00
754.00	2	Water	754.00
6.00	3	Carbopol® 940 (Goodrich)	6.00
20.00	4	Sodium hydroxide solution 10%	20.00
15.00	5	Kollidon® 30	15.00
200.00	6	Water	200.00

MANUFACTURING DIRECTIONS

Prepare solution of item 1 in item 2 by heating to 70°C, and add item 3 slowly to obtain a homogeneous suspen-

sion. Add items 4 to 6. A clear, colorless, adhesive gel is obtained. Addition of sodium chloride changes consistency.

Urea Peroxide Ear Drops

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
65.00	1	Urea peroxide (40% excess)	91.00
15.00	2	Sodium citrate (dihydrate, powder)	15.00
5.00	3	Polysorbate 20 (Tween 20)	5.00
2.50	4	Tartaric acid (12663)	2.50
QS	5	Anhydrous glycerin	QS
QS	6	Nitrogen	QS

MANUFACTURING DIRECTIONS

Add 500 mL of glycerine into a suitable tank. Start mixing at slow speed, and heat the contents to 70 to 75°C. Flood tank with nitrogen, increase mixing speed, and slowly add sodium citrate. Add tartaric acid. Mix for at least 30 minutes or until dissolved. Maintain the temperature at 70 to 75°C. When sodium citrate is completely dissolved, cool to 25 to 30°C with constant mixing. Prepare urea peroxide by breaking up lumps and screening to remove large particles. Wear gloves. Add an additional 250 to 300 mL of glycerin

into tank. Add urea peroxide slowly to prevent lumping, while mixing constantly. Mix at high speed after addition. Add Polysorbate 20 with constant mixing, and QS to final volume with glycerin. Mix for at least 30 minutes and until solution is clear. Pass solution through an approximately #100-mesh (150-µm or similar) screen, and collect in clean, dry carboys. (The filter support screen in a millipore holder may be used for filtering; the solution is too viscous to flow through a membrane or any cellulosic filter.)

Valeriana and Passiflora Extract Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
44.00	1	Valeriana extract, powder	44.00
33.00	2	Passiflora extract, powder (with excess)	36.00
120.00	3	Avicel™ PH101	120.00
11.00	4	Kollidon® CL	11.00
3.60	5	Aerosil® 200	3.60
7.30	6	Magnesium stearate	7.30

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with low compressive force. Compress 231 mg using 9-mm biconvex punches.

Vitamin A and Vitamin D Infant Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
1500 IU	1	Vitamin A palmitate (1.7 MM IU/g) (50% excess)	1.323
400 IU	2	Vitamin D (40 MM IU/g) (Cholecalciferol) (25% excess)	0.012
10.00	3	Polysorbate 80 (Tween 80)	10.00
0.88	4	Vitamin E (oily; α -tocopheryl acetate)	0.88
0.50	5	Edetate disodium (sodium EDTA)	0.50
1.00	6	Ascorbic acid	1.00
0.10	7	Saccharin sodium	0.10
600.00	8	Glycerin (glycerol)	600.00
100.00	9	Sorbitol (70% solution)	100.00
50.00	10	Propylene glycol	50.00
1.00	11	Flavor	1.00
1.50	12	Flavor	1.50
QS	13	Dye	QS
QS	14	Dye	QS
—	15	Purified water	QS to 1 L

MANUFACTURING DIRECTIONS

This product is a microemulsion and thermolabile preparation. The temperature of solution must not exceed 25°C at the time of processing. Store bulk at a temperature of 15 to 20°C under nitrogen protection. Period of storage should not exceed 48 hours prior to filling in the bottle. Collect 200.0 g of purified water in a melting vessel. Heat to 90 to 95°C for 10 minutes, and then cool to 20 to 25°C. Bubble nitrogen gas into purified water for 20 minutes. Load 100.0 g of purified water into the manufacturing vessel. Bubble nitrogen gas during all stages of the processing. Add items 5, 6, and 7, one by one, to the manufacturing vessel while mixing. Check that all materials are dissolved completely. Add items 8 and 9 and 20.0 g of item 10, one by one, to the manufacturing vessel while mixing at slow speed. Mix for 5 minutes. Avoid aeration.

Add item 3 in a stainless steel container. Mix items 1, 2, and 4, one by one, using a stirrer. Mix for 1 hour at slow speed. Avoid aeration. Add the oil phase to the aqueous phase in the manufacturing vessel at a rate of 4 mL per minute while mixing; keep on bubbling nitrogen gas throughout the process. Dissolve items 11 and 12 in 30.0 g of item 10 in a stainless steel container by slow stirring. Add to manufacturing vessel while mixing. Dissolve items 14 and 13 in 40.0 g of purified water (25 to 30°C) in a stainless steel container with slow stirring. Add to manufacturing vessel while mixing. Adjust the volume to 1.0 L with cooled purified water. Check and record the volume and pH (limit: 2.5 to 4.8). Filter the solution through a prefilter and 0.2- μ m membrane filter into the receiving tank. Bubble with nitrogen gas for 15 minutes. Store the solution with a nitrogen blanket.

Vitamin A and Vitamin D3 Drops

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/L (g)
30,000 IU	1	Vitamin A palmitate (1.7 MM IU/g)	1.90
3000 IU	2	Vitamin D3 (40 MM IU/g)	7.50 mg
12.00	3	Cremophor (relative humidity, 40%)	12.00
0.30	4	Butylhydroxytoluene	0.30
10.00	5	Lutrol E 400	10.00
0.80	6	Parabene	0.80
0.20	7	Sorbic acid	0.20
QS	8	Water	QS to 1 L

MANUFACTURING DIRECTIONS

Heat mixture of items 1 to 5 and solution of items 6 to 8 to about 65°C, and add this slowly to the well-stirred mixture of items 1 to 5. Clear or slightly opalescent yellow liquid is obtained.

Vitamin A and Vitamin D3 Oral Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (mg)
1000 IU	1	Vitamin A palmitate (1.7 MM IU/g)	60.00
100 IU	2	Vitamin D3 (40 MM IU/g)	0.30
0.002	3	Butylhydroxytoluene	0.20
3.00	4	Cremophor EL or cremophor (relative humidity, 40%)	3.00 g
QS	5	Preservative	QS
QS	6	Flavor	QS
QS	7	Water	QS to 1 L

MANUFACTURING DIRECTIONS

Heat mixture of items 1 to 4 to about 65°C, stir well, and slowly add the hot solution of item 5 (65°C). Cool to room temperature, and add item 6 to obtain a clear, yellow liquid.

Vitamin A and Vitamin D3 Syrup

Bill of Materials			
Scale (/mL)	Item	Material Name	Quantity/L (g)
30,000 IU	1	Vitamin A palmitate (1.7 MM IU/g)	19.00
10,000 IU	2	Vitamin D3 (40 MM IU/g)	0.25
70.00 mg	3	Cremophor (relative humidity, 40%)	7.00
QS	4	II. Sugar syrup (50%)	QS to 1 L

MANUFACTURING DIRECTIONS

Heat mixture of items 1 to 3 to about 45°C, stir well, and slowly add item 4 to obtain a clear, yellow liquid (pH 6.2).

Vitamin A and Vitamin E Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
5000 IU	1	Vitamin A palmitate (1.7 MM IU/g)	3.33
50.00	2	Vitamin E acetate	60.00
150.00	3	Cremophor (relative humidity, 40%)	150.00
150.00	4	Ethanol (96%)	150.00
QS	5	Water	QS to 1 L

MANUFACTURING DIRECTIONS

Heat mixture of items 1 to 3 to about 65°C, stir well, and slowly add the mixture of items 4 and 5. Color is yellow; clarity is clear (turbidity units, 25 FTU). It must be deter-

mined whether or not the ethanol concentration has a sufficient preservative efficiency. The addition of butylhydroxytoluene as an antioxidant is recommended.

Vitamin A and Vitamin E Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L
25,000 IU	1	Vitamin A palmitate (1.7 Mio IU/g)	1.50
50.00	2	Vitamin E acetate	5.00
210.00	3	Cremophor (relative humidity, 40%) ^a	21.00
QS	5	Preservative	QS
QS	6	Water	71.50

^a The quantity is reduced by 1.0 g if 1.0 g of *d,l*- α -tocopherol is also added in the formulation.

MANUFACTURING DIRECTIONS

Mix the vitamins with cremophor (and *d,l*- α -tocopherol, if used) at 60°C and then add solution of preservatives (at

37°C) slowly, with stirring to produce clear, yellow, viscous liquids.

Vitamin A and Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
33,000 IU	1	Vitamin A acetate (dry powder, 500,000 IU/g)	69.00
70.00	2	Vitamin E acetate (dry powder)	70.00
146.00	3	Mannitol (granulated) with 10% of Kollidon® 30	146.00
17.00	4	Kollidon® CL	17.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with high compressive force. Compress 300 mg in 12-mm biplanar punches.

Vitamin A Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100,000 IU	1	Vitamin A acetate (dry powder, 325,000 IU/g)	350.00
350.00	2	Mannitol	350.00
25.00	3	Kollidon® VA 64	25.00
5.00	4	Magnesium stearate (Merck)	5.00
3.00	5	Aerosil® 200	3.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with medium compressive force. Compress 750 mg in 12-mm biplanar punches.

Vitamin A Concentrate, Water-Miscible

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
100,000 IU	1	Vitamin A palmitate (1.7 MM IU/g)	6.50
2.00	2	Butylhydroxytoluene	0.20
210.00	3	Cremophor (relative humidity, 40%)	21.00
QS	4	Preservative	QS
QS	5	Water	QS to 1 L

MANUFACTURING DIRECTIONS

Heat the mixture of items 1 to 3 to about 65°C, stir well, and very slowly add the warm solution of items 4 and 5 (65°C) to obtain a clear, yellow liquid that is miscible with water.

Vitamin A Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/1000 Tablets (g)
50,000 IU	1	I. Vitamin A palmitate (1.7 Mio IU/g)	3.00
110.00	2	Cremophor (relative humidity, 40%)	11.00
1.00	3	Butylhydroxytoluene	0.10
QS	4	Water	85.90

MANUFACTURING DIRECTIONS

Heat the mixture of items 1 to 3 to about 65°C, stir very well, and slowly add the hot water (65°C) to obtain a clear or slightly opalescent yellow solution of low viscosity. Lutrol E 400 can be added at a level of 5% (compensated for by item 4).

Vitamin A Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Quantity/1000 Suppositories (g)
150,000 IU	1	Vitamin A palmitate (1.7 MM IU/g)	88.23
1.00	2	Butylhydroxytoluene	10.00
400.00	3	Cremophor (relative humidity, 40%)	400.00
800.00	4	Lutrol E 1500	800.00
500.00	5	Lutrol E 4000	505.00

MANUFACTURING DIRECTIONS

Dissolve butylhydroxytoluene in the warm vitamin A. Add cremophor, and mix with the molten Lutrol E grades. Fill into molds of suppositories to obtain a weight of 2 g.

Vitamin A Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50,000 IU	1	Vitamin A acetate (dry powder, 500,000 IU/g)	110.00
100.00	2	Avicel™ PH102	100.00
10.00	3	Kollidon® VA 64	10.00
5.00	4	Kollidon® CL	5.00
1.00	5	Aerosil® 200	1.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with low compressive force. Compress 231 mg using 9-mm binconvex punches.

Vitamin A Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5000	1	Vitamin A acetate (dry powder, 500,000 IU/g)	110.00
189.00	2	Ludipress®	189.00
1.00	3	Magnesium stearate (Merck)	1.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with low compressive force. Compress 306 mg in 8-mm punches.

Vitamin A Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50,000	1	Vitamin A acetate (dry powder, 500,000 IU/g)	120.00
120.00	2	Ludipress®	120.00
10.00	3	Avicel™ PH101	10.00
1.00	4	Magnesium stearate (Merck)	1.00
1.00	5	Aerosil® 200	1.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with low compressive force. Compress 277 mg in 8-mm punches.

Vitamin A Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50,000	1	Vitamin A acetate (dry powder, 500,000 IU/g)	110.00
154.00	2	Avicel™ PH101	154.00
10.00	3	Kollidon® VA 64	10.00
4.00	4	Kollidon® CL	4.00
1.00	5	Aerosil® 200	1.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press with low compressive force. Compress 250 mg in 8-mm punches.

Vitamin A Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25,000 IU	1	Vitamin A acetate (dry powder, 500,000 IU/g)	55.00
572.00	2	Dicalcium phosphate (granulated) (Di-Tab) with 3% of Kollidon® 30	572.00
28.00	3	Polyethylene glycol, powder	28.00
19.40	4	Kollidon® CL	19.40
5.60	5	Aerosil® 200	5.60

MANUFACTURING DIRECTIONS

Granulate the dicalcium phosphate with Kollidon 30, dissolved in isopropanol or water, and pass through a 0.5-mm screen. Mix the obtained dried granules with the other

components, sieve, and press with high compressive force using a vibrating hopper. Compress 680 mg in 12-mm biplanar punches.

Vitamin A, Vitamin B6, and Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
40,000 IU	1	Vitamin A acetate (dry powder, 500,000 IU/g)	80.00
40.00	2	Pyridoxine hydrochloride	40.00
35.00	3	Vitamin E acetate (dry powder, SD 50)	75.00
395.00	4	Ludipress®	395.00
4.00	5	Magnesium stearate	4.00
5.00	6	Aerosil® 200	5.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with high compressive force. Compress 583 mg in 12-mm biplanar punches.

Vitamin A, Vitamin C, and Vitamin D3 Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2000/200 IU	1	Vitamin A and vitamin D3 (dry powder, 500,000 and 50,000 IU/g, respectively)	4.00
30.00	2	Ascorbic acid (powder)	33.00
300.00	3	Sucrose (crystalline)	300.00
300.00	4	Sorbitol (crystalline)	300.00
300.00	5	Mannitol	300.00
300.00	6	Ludipress®	300.00
5.00	7	Stearic acid	5.00
0.10	8	Saccharin sodium	0.10
30.00	9	Cyclamate sodium	30.00
30.00	10	Flavor mixture (Firmenich)	30.00
20.00	11	PEG-6000, powder	20.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with high compressive force. Compress 1290 mg in 16-mm biplanar punches.

Vitamin A, Vitamin C, and Vitamin E Tablets (1200 IU/60 mg/30 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets
1200 IU	1	Vitamin A acetate (dry powder, 500,000 IU/g)	2.40
60.00	2	Ascorbic acid (powder)	60.00
30.00	3	Vitamin E acetate (dry powder, 50%)	60.00
105.00	4	Lactose monohydrate	105.00
30.00	5	Avicel™ PH101	30.00
20.00	6	Kollidon® 25	20.00
5.00	7	Talc	5.00
1.00	8	Aerosil® 200	1.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with medium compression force. Compress 285 mg in 8-mm biplanar punches.

Vitamin B-Complex, Amino Acids, and Magnesium Effervescent Granules (Sugar-Free)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.00	1	Thiamin hydrochloride	2.00
2.00	2	Pyridoxine hydrochloride	2.00
5.00	3	Cyanocobalamin (dry powder, 0.1%)	5.00
20.00	4	L-glutamine	20.00
10.00	5	Inositol	10.00
10.00	6	Potassium L-aspartate	10.00
500.00	7	<i>d,l</i> -Carnitine hydrochloride	500.00
350.00	8	Magnesium L-aspartate	350.00
600.00	9	Anhydrous citric acid	600.00
500.00	10	Sodium bicarbonate	500.00
QS	11	Flavors	QS
50.00	12	Kollidon® VA 64	50.00
80.00	13	Isopropanol	80.00

MANUFACTURING DIRECTIONS

Mix items 1 to 6, add the mixture of items 7 to 12, granulate the mixture of these two combinations with item

13, pass through an 0.8-mm sieve, dry well, and mix. Fill 2.1 g of the granules into sachets.

Vitamin B-Complex and Carnitine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
95.00	1	Thiamine mononitrate	95.00
20.00	2	Riboflavin	20.00
100.00	3	Nicotinamide	100.00
50.00	4	Calcium D-pantothenate	50.00
2.00	5	Folic acid	2.00
0.20	6	Biotin	0.20
0.005	7	Cyanocobalamin (gelatin coated, 1%)	0.50
50.00	8	Carnitine hydrochloride	50.00
100.00	9	Inositol	100.00
2.00	10	Adenosine phosphate	2.00
15.70	11	Kollidon® 30	15.70
70.00	12	Isopropanol	70.00
26.00	13	Kollidon® CL	26.00
122.00	14	Lactose monohydrate	122.00
14.00	15	PEG-6000, powder	14.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 10 with solution of items 11 and 12. Dry, pass through an 0.8-mm sieve, mix with items 13 and 15, and press with low compressive force. Compress 708 mg using 13-mm binplanar punches.

Vitamin B-Complex and Folic Acid Dragees

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
4.35	1	Calcium D-pantothenate (granulate, 67%)	6.50
2.60	2	Thiamine mononitrate (10.4%)	25.00
20.00	3	Magnesium oxide (light)	20.00
45.75	4	D-mannitol (powder)	45.75
100.00	5	DL-methionine	100.00
2.30	6	Riboflavin	2.30
6.30	7	Nicotinamide	6.30
2.40	8	Pyridoxine HCl	2.40
4.00	9	Magnesium stearate	4.00
0.1150	10	D-biotin	0.1150
0.46	11	Folic acid	0.46
100.00	12	Choline tartarate	100.00
28.00	13	Silicic acid (precipitated)	28.00
0.87 mcg	14	Vitamin B12 (as 0.1% water soluble form)	0.871
3.15	15	Vitamin E (50%)	6.30
30.00	16	Sodium carboxymethyl starch	30.00
116.66	17	Isopropyl alcohol	116.66
22.00	18	Povidone (PVK K-90) (Luviskol®)	22.00

MANUFACTURING DIRECTIONS

Incorporate in mixer PVP K-90 and isopropyl alcohol, and make a solution with continuous stirring. Place in mixer choline tartarate, DL-methionine, D-mannitol powder, magnesium oxide (previously sieved), silicic acid, and sodium carboxymethyl starch, and mix for 15 minutes. Add the solution of isopropyl alcohol and alcohol in first step for 10 minutes until moist mass is obtained. Granulate the moist mass through a centrifugal granulator with a 10-mm screen. Spread the granules on paper-lined trays, and dry overnight in a drying oven at 50°C. Crush the granules through a 1.5-mm sieve. *Vitamin granulate:* Tumble D-biotin, vitamin B12, folic acid, riboflavin, and pyridoxine hydrochloride in mixer for 5 minutes. Combine in the mixer the nicotinamide, vitamin E, thiamine mononitrate/gelatin/mannitol granulate, D-mannitol powder, and sodium carboxymethyl starch, then add the vitamin mix-

ture, and mix for 10 minutes. Pass through a 1-mm sieve if lumpy. In a mixer, make a separate solution of PVP K-90 and isopropyl alcohol. Place in the mixer the solution of isopropyl alcohol and PVP, then knead until an evenly moist homogeneous mass is obtained. Add calcium-D-pantothenate granules, and mix for 3 to 5 minutes. Pass the granules through a centrifugal granulator with a 10-mm screen, and spread on paper-lined trays. Keep overnight in a drying oven at 50°C; the relative humidity of the granules should be 10 to 20%. Crush the dried granules through an oscillator with a 1.5-mm sieve. Put the granulate mixture in the mixing drum — the choline tartarate and the two lots of vitamin granules. Mix, and then add the magnesium stearate. Check to be sure that the relative humidity of the mixture is 10 to 20%. Compress, and apply a sealer coat (lacquer), sugar coat, and finishing coating.

Vitamin B-Complex and Iron Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
910.00	1	Sorbitol solution	910.00
0.019	2	Propyl paraben	0.019
0.17	3	Methyl paraben	0.17
1.50	4	Niacinamide (white powder)	1.50
0.30	5	Riboflavin	0.30
103.60	6	Propylene glycol	103.60
126.40	7	Glycerin	126.40
26.13	8	Iron sulfate (granular)	26.132
0.037	9	Dye	37.50 mg
0.25	10	Pyridoxine hydrochloride	0.25
1.20	11	Saccharin sodium (dihydrate powder)	1.20
22.00	12	Sodium cyclamate (powder)	22.00
30.00	13	Ascorbic acid (white powder)	30.00
0.80	14	Sodium bicarbonate (powder)	0.80
0.36	15	Thiamine hydrochloride (powder, regular)	0.36
0.625	16	D-Pantothenyl alcohol (dexpantenol)	0.62
0.002	17	Vitamin B12 (cyanocobalamin)	2.00 mg
0.007	18	Flavor	0.70 mL
QS	19	Deionized purified water	QS to 1 L
QS	20	HyFlo filter aid	QS
QS	21	Hydrochloric acid	QS
QS	22	Sodium hydroxide	QS

MANUFACTURING DIRECTIONS

Manufacture under complete carbon dioxide (CO₂) protection. Load 780 g (portion of item 2) of sorbitol solution into a jacketed, stainless steel tank; the remaining sorbitol will be used later. Add parabens (unless added previously), niacinamide, and riboflavin to the sorbitol or glucose solution. Heat solution to 85 to 90°C, and mix until the ingredients are dissolved. Remove heat. While mixing, cool the main solution to 50 to 60°C. Hold at this temperature while bubbling CO₂ into it. CO₂ protection must be continued for the remainder of the manufacturing procedure. Heat 50 mL of purified water to boiling, and bubble CO₂ into it while cooling to 55°C. Add and dissolve, with mixing, iron sulfate with 30 mL of purified water at 55°C. Use CO₂ protection. Warm the solution to 50 to 55°C while mixing to dissolve, then slowly add the solution, with good mixing, to the solution above. The above addition should be made as soon as possible to prevent oxidation. Add the pyridoxine, saccharin sodium and sodium cyclamate, and mix until dissolved. Cool the solution to 30°C. Add the ascorbic acid, with good stirring, to 78 g of reserved sorbitol; make a slurry. Use a container that has plenty of headspace. Then add the sodium bicarbonate slowly in small portions to the ascorbic acid slurry, with stirring,

until all of the powder has been added and most of the foaming has stopped. Add this slurry slowly to the solution from the step above with vigorous mixing until a uniform solution results. Rinse the mixing container with 22 g of the reserved sorbitol, and add to the product with stirring. Add and dissolve thiamine hydrochloride with mixing. If necessary, warm the D-pantothenyl alcohol until liquified, and add it to the 0.5-mL CO₂-saturated purified water. Use an additional 0.5 mL of CO₂-saturated purified water to thoroughly rinse the container of D-pantothenyl alcohol, and add this to the D-pantothenyl alcohol solution. Mix the D-pantothenyl alcohol solution thoroughly until it is homogeneously dispersed. Add the D-pantothenyl alcohol solution to the main solution with mixing. Use an additional 0.5 mL of CO₂-saturated purified water to rinse out the container in which the D-pantothenyl alcohol solution was made, and add to the product with mixing. Dissolve the vitamin B12 in 0.5 mL of purified water to make a clear solution, and add this to the product with good mixing. Dissolve the guarana flavor in the 10 g of propylene glycol, reserved from earlier step, with good stirring. Add this solution to the product with good mixing. Check pH (range: 3.00 to 3.30). Adjust, if necessary, with a solution of 10% sodium hydroxide or 10% hydrochloric acid depending on the test results. Adjust the volume of the

product with the remaining 30 g of the sorbitol solution and, if necessary, purified water to 1 L. Mix for 1 hour. Allow to stand overnight to eliminate entrapped CO₂ gas. Readjust volume to 1 L with purified water. Mix for 1 hour. Filter by adding HyFlo filter aid and mixing it,

followed by passing through a filter press. Do not allow temperature to exceed 30°C. Bubble CO₂ gas into clear filtrate for 5 minutes, then seal tank, and hold product under CO₂ protection.

Vitamin B-Complex and Vitamin C Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
33.00	1	Thiamine mononitrate	33.00
4.00	2	Riboflavin	4.00
10.00	3	Pyridoxine hydrochloride	10.00
66.00	4	Nicotinamide	66.00
17.00	5	Calcium D-pantothenate	17.00
350.00	6	Tartaric acid (powder)	350.00
450.00	7	Sodium bicarbonate	450.00
750.00	8	Sucrose, crystalline	750.00
30.00	9	Kollidon® 30	30.00
QS	10	Isopropanol	QS
500.00	11	Ascorbic acid (crystalline)	500.00
3.00 g	12	Riboflavin	3.00
10.00	13	Cyanocobalamin (gelatin-coated, 0.1%)	10.00
10.00	14	Orange flavor	10.00
2.00	15	Saccharin sodium	2.00
5.00	16	Cyclamate sodium	5.00
50.00	17	PEG-6000 (powder)	50.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 9 with solvent item 10, dry, pass through an 0.8-mm sieve, mix with items 13 to

17, and press with high compressive force at a maximum of relative atmospheric humidity of 30%. Compress 2315 mg in 20-mm biplanar punches.

Vitamin B-Complex and Vitamin C Instant Granules

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
3.60	1	Thiamine hydrochloride	3.60
5.70	2	Riboflavin phosphate sodium	5.70
45.00	3	Nicotinamide	45.00
4.50	4	Pyridoxine hydrochloride	4.50
15.0	5	Cyanocobalamin (gelatin-coated, 0.1%)	15.00
150.0	6	Ascorbic acid (powder)	150.00
723.00	7	Sucrose	723.00
51.00	8	Kollidon® 30	51.00
QS	9	Ethanol	180 mL

MANUFACTURING DIRECTIONS

Mix items 1 to 7, granulate with solution of items 8 and 9, dry, and pass through an 0.8-mm sieve. Fill 1 g of the granules in sachets (or 10 g in 100 mL flakes as dry syrup) to produce yellow homogeneous granules dispersible in

cold water. About 1 g of the granules (= 1 sachet) corresponds to two daily vitamin B and vitamin C requirements of adults. Due to the high loss of riboflavin phosphate sodium, it should be substituted by riboflavin.

Vitamin B-Complex and Vitamin C Syrup

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
0.60	1	Thiamine hydrochloride	0.60
0.55	2	Riboflavin phosphate sodium	0.55
2.50	3	Nicotinamide	2.50
1.20	4	Dexpantenol	1.20
0.55	5	Pyridoxine hydrochloride	0.55
9.00	6	Ascorbic acid (crystalline)	9.00
0.25	7	Orange flavor	0.25
0.05	8	EDTA sodium	0.05
0.50	9	Propyl gallate	0.50
2.00	10	Sorbic acid	2.00
5.00	11	Kollidon® 25	5.00
10.00	12	Sorbitol (crystalline)	10.00
9.00	13	Glycerol	9.00
10.00	14	1,2-Propyleneglycol (Pharma)	10.00
5.00	15	Water	5.00
QS	16	Sugar syrup (64% sucrose in water)	QS to 1 kg

MANUFACTURING DIRECTIONS

Mix solution of items 1 to 5 with sugar syrup, adjust the clear solution to about pH 4.2, and use nitrogen as an inert

gas in the final packaging; 10 g provides two to three RDA.

Vitamin B-Complex and Vitamin C Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
0.15	1	Thiamine hydrochloride	0.15
0.15	2	Riboflavin phosphate sodium	0.15
0.70	3	Nicotinamide	0.70
0.035	4	Dexpanthenol	0.035
0.150.00	5	Pyridoxine hydrochloride	0.15
2.25	6	Ascorbic acid (crystalline)	2.25
0.28	7	Orange aroma	0.28
0.56	8	EDTA sodium	0.56
186.50	9	Propylene glycol (Pharma) + water (2:1)	186.50
0.15	10	Parabene	0.15
84.30	11	Sorbitol (crystalline)	84.30
562.50	12	Sucrose (crystalline)	562.50
42.00	13	Water	42.00

MANUFACTURING DIRECTIONS

Dissolve items 1 to 8 in item 2. Prepare a solution of items 10 to 13 by heating. Cool, and mix with solution of the

balance of the formulation. Adjust to a pH of 4.2 to 4.5. Adjust volume with water; use more, if necessary. Use nitrogen as an inert gas during packaging.

Vitamin B-Complex and Vitamin C Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Thiamine mononitrate	5.00
5.00 g	2	Riboflavin	5.00
5.00	3	Pyridoxine hydrochloride	5.00
0.50	4	Folic acid	0.50
30.00	5	Niacin	30.00
0.10	6	Biotin	0.10
10.00	7	Calcium D-pantothenate	10.00
150.00	8	Ascorbic acid (crystalline/powder)	150.00
172.40	9	Ludipress®	172.40
20.00	10	Kollidon® VA 64	20.00
2.00	11	Magnesium stearate	2.00

MANUFACTURING DIRECTIONS

Mix all ingredients and pass through an 0.8-mm sieve, and mix. Use medium to low compressive force to compress 400 mg in 10-mm biplanar punches.

Vitamin B-Complex and Vitamin C Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
15.00	1	Thiamine hydrochloride	15.00
2.00	2	Riboflavin	2.00
5.00	3	Pyridoxine hydrochloride	5.00
25.00	4	Choline bitartrate	25.00
10.00	5	Nicotinamide	10.00
100.00	6	Ascorbic acid (crystalline/powder)	100.00
220.00	7	Ludipress®	220.00
8.00	8	Stearic acid	8.00

MANUFACTURING DIRECTIONS

Mix all ingredients and pass through an 0.8-mm sieve, and mix. Use medium to low compressive force to com-

press 411 mg in 12-mm biplanar punches. The thiamine mononitrate formulation is more stable compared with the thiamine hydrochloride formulation (above).

Vitamin B-Complex, Choline, and Bile Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
60.00	1	Acid dehydrochloric (powder)	60.00
100.00	2	Choline dihydrogen citrate	100.00
20.00	3	Niacinamide (white powder)	20.00
100.00	4	Inositol	100.00
2.50	5	Riboflavin (2% excess)	2.55
0.50	6	Pyridoxine hydrochloride	0.50
30.00	7	Povidone (<i>K</i> value, 29 to 32)	30.00
100.00	8	Racemethionine (crystals)	100.00
60.00	9	Ox bile extract (powder, #30-mesh) (Bilein)	60.00
—	10	Alcohol dehydrated (200 proof)	26.00
3.0 µg	11	Cyanocobalamin (oral powder in gelatin, 1000 µg/g)	3.30
3.00	12	Thiamine hydrochloride (powder, regular)	3.60
8.40	13	Magnesium stearate (impalable powder)	8.40
8.40	14	Stearic acid (fine powder)	8.40

MANUFACTURING DIRECTIONS

Mill dehydrochloric acid, choline dihydrogen citrate, nicotinamide, inositol, and methionine through a 600-µm screen. Charge milled mixture from first step with riboflavin, pyridoxine hydrochloride, Povidone, and ox bile extract in mass mixer. Add alcohol QS (approximately 26 g or 32.7 mL) very slowly to the mass. Mass for approximately 45 minutes in mixer. Scrape all material from the mass mixer as much as possible. Rinse mass mixer between runs. Granulate through a comminuting or similar mill or a 4.76-mm screen. Dry at 49°C to less than 1% LOD. Sift through an 840-µm screen in a shaker and grind coarsely through a comminuting

mill (knives forward, medium speed). Charge one half of the base granulation through a 1.68-mm screen into a blender, if necessary. Mix cyanocobalamine oral powder with an equal volume of base granulation, and charge into a blender through a 1.68-mm screen. Blend thiamine hydrochloride, magnesium stearate, and stearic acid. Then hand-screen mixture through a 600-µm screen. Load into a blender through a 1.68-mm screen with the remainder of the base granulation, and blend for 20 minutes. Compress and coat tablets using an appropriate formulation to render required color and sealing of tablet.

Vitamin B-Complex Syrup

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
0.60	1	Thiamine hydrochloride	0.60
0.55	2	Riboflavin 5-phosphate sodium	0.55
2.50	3	Nicotinamide	2.50
1.20	4	Dexpantenol	1.20
0.55	5	Pyridoxine hydrochloride	0.55
2.00	6	Sorbic acid	2.00
0.05	7	EDTA sodium	0.05
2.25	8	Vanillin	2.25
465.00	9	Sucrose	465.00
25.00	10	Kollidon® 25	25.00
90.00	11	Glycerol	90.00
100.00	12	Propylene glycol (Pharma)	100.00
310.00	13	Water	310.00

MANUFACTURING DIRECTIONS

Dissolve the sucrose in the heat mixture of glycerol, propylene glycol, and water; cool to room temperature, and dissolve the other components to obtain a clear solution.

Vitamin B-Complex Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
0.66	1	Dexpanthenol	0.66
4.40	2	Nicotinamide	4.40
0.22	3	Pyridoxine hydrochloride	0.22
0.60	4	Riboflavin- 5-phosphate sodium	0.60
1.50	5	Thiamine hydrochloride	1.50
350.00	6	Sorbitol (70% solution)	350.00
11.20	7	Propylene glycol	11.20
0.84	8	Methyl paraben	0.84
0.168	9	Propyl paraben	0.168
550.00	10	Maltitol solution (Lycasin 80/55)	550.00
0.15	11	Edetate disodium (sodium EDTA)	0.15
3.72	12	Citric acid (monohydrate)	3.72
3.72	13	Sodium citrate	3.72
2.50	14	Sodium benzoate	2.50
0.50	15	Saccharin sodium	0.50
150.00	16	Glycerin (glycerol)	150.00
1.50	17	Flavor	1.50
1.00	18	Flavor	1.00
—	19	Purified water	QS to 1 L

MANUFACTURING DIRECTIONS

Load items 6, 10, and 16 in a manufacturing vessel, and mix for 5 minutes. Dissolve items 8 and 9 in item 7 in a stainless steel container. Put the entire container in hot water (60 to 70°C), and stir to dissolve. Add the clear solution to the mixer. Dissolve items 11 and 12 in 40.0 g of purified water in a stainless steel container. Add the clear solution to the mixer. Dissolve items 14, 13, and 15 in 50.0 g of purified water in a stainless steel container. Add the clear solution to mixer, and mix for 5 minutes. Dissolve item 1 in 10.0 g of purified water in a stainless steel container. Add the clear solution to mixer. Dissolve items 5 and 3 in 10.0 g of purified water in a stainless

steel container. Add the clear solution to mixer. Dissolve items 2 and 4 in 30.0 g of purified water in a stainless steel container. Add the clear yellow solution to mixer, and mix for 5 minutes. Add items 17 and 18 to mixer. Bring the volume up to 1 L with purified water, and finally mix for 15 to 20 minutes. Check and record the pH (limit: 4.4 to 4.8 at 25°C). If required, adjust pH with 20% citric acid or 20% sodium citrate solution. Filter the syrup at 1.5 bar. Recirculate about 200 to 300 mL syrup. Transfer the filtered syrup to the storage vessel, flushing with nitrogen gas. Store the syrup under a nitrogen blanket for not more than 2 days prior to filling.

Vitamin B-Complex Syrup (without B12)

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
570.00	1	Sucrose	570.00
70.00	2	Glycerin (glycerol)	70.00
3.72	3	Citric acid (monohydrate)	3.72
1.00	4	Edetate disodium (sodium EDTA)	1.00
0.90	5	Calcium pantothenate (10% excess)	1.00
5.70	6	Sodium citrate	5.70
0.84	7	Methyl paraben	0.84
0.168	8	Propyl paraben	0.168
1.90	9	Benzoic acid	1.90
1.14	10	Strawberry flavor manefils	1.14
9.60	11	Alcohol (ethanol, 95%)	9.60
1.50	12	Thiamine hydrochloride (50% excess)	1.50
0.20	13	Pyridoxine hydrochloride (10% excess)	0.22
4.00	14	Nicotinamide (10% excess)	4.40
0.30	15	Riboflavin sodium phosphate (50% excess)	0.60
QS	16	Purified water	QS to 1 L

MANUFACTURING DIRECTIONS

Flush with nitrogen gas (purity 99.95%). Add 400.0 g of purified water to the manufacturing vessel, and heat to 90 to 95°C. Add item 1 while mixing at low speed. After addition of item 1, mix for 30 to 35 minutes at high speed (temperature, 90 to 95°C). Cool to 40°C while mixing at low speed. Disperse 1.0 g of filter aid in 10.0 g of cooled purified water (25 to 30°C) in a stainless steel container to prepare a slurry. Add the slurry to the syrup in syrup vessel. Mix for 15 minutes at high speed. Filter the syrup at 1.5 bar. Recirculate about 40 to 60 mL syrup. Transfer the filtered syrup to the storage vessel. Recharge the filtered syrup to the manufacturing vessel. Start mixing. Add item 2 to the syrup vessel while mixing at high speed. Add item 3 to the syrup vessel while mixing to dissolve at high speed. Dissolve item 4 in 6.0 g of cooled purified water (25 to 30°C), and add to the syrup vessel while mixing at high speed. Dissolve item 5 in 6.0 g of cooled purified water, and add to the syrup vessel while mixing at high speed for 30 minutes. Dissolve item 6 in 10.0 g of cooled purified water (25 to 30°C), and add to the syrup vessel while mixing at high speed. Dissolve items 7 to 10 in item 11 in a stainless steel container, and add to the syrup vessel while mixing at high speed for 15 minutes. Dissolve items 12 and 13 in 6.0 g of cooled purified water

(25 to 30°C) in a separate stainless steel container, and add to the syrup vessel while mixing at high speed. Rinse the container with 1.0 g of cooled, purified water (25 to 30°C), and add the rinsing to the syrup vessel while mixing at high speed. Flush the vessel with nitrogen gas (purity 99.95%) for 15 minutes. Dissolve item 14 in 9.0 g of cooled purified water in a separate stainless steel container, and add to the syrup vessel while mixing at high speed. Rinse the container with 1.0 g of cooled purified water (25 to 30°C), and add the rinsing to the syrup vessel while mixing at high speed. Dissolve item 15 in 4.0 g of cooled, purified water (25 to 30°C) in a separate stainless steel container, and add to the syrup vessel while mixing at high speed. Rinse the container with 1.0 g of cooled, purified water, and add the rinsing to the syrup vessel while mixing at high speed. Bring the volume up to 1 L with cooled, purified water (25 to 30°C), and finally mix for 15 minutes at high speed. Check and record the pH (limit: 4.3 to 4.7 at 25°C). If required, adjust pH with 10% solution of citric acid or sodium citrate. Flush the syrup with nitrogen gas (purity 99.95%) for 15 minutes. Close the tank. Hold the syrup for 12 hours. Filter the syrup at 1.5 bar. Recirculate about 40 to 60 mL syrup. Transfer the filtered syrup to the storage vessel.

Vitamin B-Complex Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Thiamine mononitrate or hydrochloride	25.00
25.00	2	Riboflavin	25.00
80.00	3	Nicotinamide	80.00
40.00	4	Calcium D-pantothenate	40.00
16.00	5	Pyridoxine hydrochloride	16.00
0.16	6	Cyanocobalamin (gelatin-coated, 0.1%)	16.00
282.00	7	Avicel™ PH101	282.00
16.00	8	Kollidon® 30	16.00
3.00	9	Aerosil® 200	3.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with medium to high compressive force. Compress

513 mg for mononitrate and 504 mg for hydrochloride tablets in 12-mm biplanar punches. (The mononitrate formulation is preferred for stability reasons.)

Vitamin B-Complex Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.30	1	Thiamine mononitrate	2.30
2.60	2	Riboflavin	2.60
2.30	3	Nicotinamide	2.30
2.20	4	Calcium D-pantothenate	2.20
2.70	5	Pyridoxine hydrochloride	2.70
0.024	6	Cyanocobalamin (gelatin-coated, 0.1%)	2.40
280.00	7	Ludipress®	280.00
14.00	8	Flavor (Firmenich)	14.00
0.050	9	Saccharin sodium	0.05
4.00	10	Cyclamate sodium	4.00
5.00	11	Magnesium stearate	5.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with low compressive force. Compress 314 mg using

8-mm biplanar punches. (According to European Commission, this formulation is classified as dietary food.)

Vitamin B-Complex Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
15.00	1	Microcrystalline cellulose (Avicel™ PH102)	15.00
0.20	2	Colloidal silicon dioxide (Aerosil® 200)	0.20
3.00	3	Calcium pantothenate	3.00
9.33	4	Powdered cellulose	9.33
35.60	5	Lactose (spray-dried)	35.60
0.91	6	Magnesium stearate	0.91
20.00	7	Nicotinamide	20.00
2.10	8	Pyridoxine hydrochloride	2.10
2.00	9	Riboflavine base	2.00
0.80	10	Talc (fine powder)	0.80
2.10	11	Thiamine mononitrate	2.10

MANUFACTURING DIRECTIONS

Riboflavine base is a fine powder that tends to form globules while mixing. Disperse the base with Aerosil and lactose carefully. Mix items 9 and 2 and 6.67 g of item 5 in the drum of a drum mixer for 10 minutes. Pass the mix two times through a 500- μ m sieve using a sifter. Pass items 11, 8, and 3 and 6.67 g of item 5 through a granulator fitted with a 1.0-mm sieve. Pass items 7, 1, and 4 and

22.27 g of item 5 through a granulator fitted with a 1.0-mm sieve. Pass items 10 and 6 through a sifter fitted with a 500- μ m sieve. Load sieved material from previous step to the blender. Load sieved material to the blender. Blend the powders for 15 minutes. Load lubricant powders into the blender, and mix for an additional 5 minutes. Compress 91 mg at low relative humidity (55 to 60%). Coat tablets with a sealing coat, color coat, and polishing coat.

Vitamin B-Complex, Vitamin A, Vitamin C, and Vitamin D Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
60.00	1	Sucrose	600.00
51.00	2	Methyl paraben	1.00
0.20	3	Propyl paraben	0.20
1.00	4	Edetate disodium (sodium EDTA)	1.00
10.00	5	Ascorbic acid (50% excess)	15.00
0.80	6	Sodium hydroxide	0.80
4.00	7	Nicotinamide (5% excess)	4.20
0.40	8	Riboflavin sodium phosphate (8% excess)	0.43
1.00	9	Thiamine hydrochloride (50% excess)	1.50
1.20	10	Pyridoxine hydrochloride (10% excess)	1.32
0.50	11	Monosodium glutamate (sodium glutamate)	0.50
1.26 mcg	12	Cyanocobalamin (50% excess)	0.0018
150.00	13	Propylene glycol	150.00
1000.0 IU	14	Vitamin A palmitate (1.75 MM IU/g) (54% excess)	0.88
100.0 IU	15	Cholecalciferol (40 MM IU/g) (52% excess)	0.0038
13.20	16	Polysorbate 80 (Tween 80)	13.20
2.50	17	Poloxyl 20 cetostearyl ether (Cetomacrogol 1000)	2.50
0.30	18	Lemon oil terpeneless	0.30
0.84	19	Strawberry oil (composed)	0.84
QS	20	Purified water	QS to 1 L

MANUFACTURING DIRECTIONS

This product is an aqueous solution of water-soluble vitamins with oily vitamin A palmitate and cholecalciferol solubilized in water using the surfactant system of Tween 80 and Cetomacrogol. This syrup is a solubilized oil surfactant system and is affected by heat and rate of mixing. The temperature of the solution must not exceed 30°C at the time of final mixing. The final mixing must be continuous, without any interruption. For the preparation of oily phase, the container must be dry. Before start of batch, cool about 80.0 mL of purified water and flush with nitrogen gas (purity, 99.95%). Use this water for making solutions and for adjusting the volume. Add 420.0 g of purified water to the manufacturing vessel and heat to 90 to 95°C. Add items 2 and 3 while mixing to dissolve. Add item 1 while mixing at slow speed. After addition of item 1, mix for 30 to 35 minutes at high speed and a temperature of 90 to 95°C. Cool to 25 to 30°C while mixing at low speed. Bubble nitrogen gas for 10 minutes. Add item 4 to the syrup while mixing at high speed to dissolve. Add item 5 to the syrup while mixing at high speed to dissolve. Add 4.00 g of purified water (25°C) in a separate container, and dissolve item 6 by using a stirrer. Transfer the cooled item 6 solution to the syrup tank while mixing at high speed. Mix for 15 minutes. Check the pH of the syrup (limit: 3.75 to 3.85). Add items 7 to 11, one by one, to the syrup in the manufacturing vessel while mixing at high

speed to dissolve. Mix for 10 minutes. Add 6.0 g of cold purified water (25°C) in a separate container, and dissolve item 12. Add to the manufacturing vessel while mixing at high speed. Rinse the container with cooled purified water (about 2 mL), and transfer the rinsing to the syrup manufacturing vessel; mix well at high speed. Add item 13 to the manufacturing vessel while mixing at high speed. Warm item 14 to 70°C in a separate stainless steel container in a water bath. Warm item 16 to 70°C, and mix well with item 14 under nitrogen atmosphere. Add item 15 while mixing. Melt item 17 in a stainless steel container, and add with stirring to mix well. Cool to 30°C while mixing under nitrogen atmosphere. Add items 18 and 19 to the oily phase solution, and mix for 15 minutes at high speed. Check and record the volume of the oily phase. Start mixing and continue mixing (*mixing must be continuous*). Start the addition of the oily phase solution in a thin stream (*do not stop mixing during addition of oily phase*). After the addition is complete, mix for an additional 15 minutes at high speed. Rinse the oily phase vessel with a sufficient quantity of syrup from the syrup vessel. Transfer the rinsing to the syrup vessel. Bring the volume up to 1 L with cooled purified water (25°C), and finally mix for 20 minutes at high speed. Check and record the pH (limit: 3.75 to 3.85 at 25°C). Filter the syrup at 1.5 bar. Recirculate about 40 to 60 mL syrup.

Vitamin B-Complex, Vitamin A, Vitamin C, and Vitamin D Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.00	1	Thiamine mononitrate (20% excess)	2.40
1.00	2	Riboflavine (10% excess)	1.10
74.50	3	Lactose (spray-dried)	74.50
15.00	4	Nicotinamide	15.00
300 IU	5	Vitamin D3 (dry powder, 100,000 IU/g)	3.60
3000 IU	6	Vitamin A palmitate (250,000 IU/g)	18.00
36.00	7	Cellulose (microcrystalline) (Avicel™ PH102)	36.00
20.00	8	Ascorbic acid (90%) (33% excess)	26.60
1.00	9	Silicon dioxide (colloidal) (Aerosil® 200)	1.00
1.80	10	Magnesium stearate	1.80

MANUFACTURING DIRECTIONS

Mix items 1 and 2 and 13.33 g of item 3 in a drum using a drum mixer for 10 minutes. Pass the mix through a 250- μ m sieve using a sifter. Collect in a stainless steel drum, and load into the blender. Pass items 4 to 7 and 61.17 g of item 3 through a granulator fitted with a 1.0-mm sieve. Collect in a stainless steel drum, and load into the blender. Pass item 8 through a Fitz mill fitted with sieve number 24230. Collect in a stainless steel drum, and load into the

blender. Mix for 10 minutes. Pass item 9 through a 500- μ m sieve using a sifter. Collect in a polyethylene bag. Pass item 10 through a 250- μ m sieve using a sifter. Collect in the same polyethylene bag. Mix and add 0.53 to 1.33 g powder from the step above. Mix gently. Add to the blender. Mix for 3 minutes. Unload lubricated granules in stainless steel drums. Compress 180 mg in 7-mm round concave punches. Apply a sealing coat, a color coat, and finishing coat (see Appendix).

Vitamin B-Complex, Vitamin A, Vitamin C, Vitamin D, and Calcium Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
675.00	1	Glycerin (96%)	675.00
16.66	2	Niacinamide (white powder)	16.66
2.73	3	Riboflavin-5'-phosphate sodium (3% excess)	2.82
0.50	4	Methyl paraben	0.50
1.00	5	Acid benzoic	1.00
105.00	6	Saccharin sodium (powder)	105.00
73.36	7	Calcium Chloride (granules, dihydrate)	73.36
28.78	8	Ferrous gluconate	28.78
2.25	9	Thiamine hydrochloride (powder, regular) (35% excess)	3.375
1.00	10	Pyridoxine hydrochloride	1.00
83.33	11	Ascorbic acid (white powder) (35% excess)	112.50
0.25	12	Oil orange terpeneless	0.25
0.081	13	Alcohol (ethanol; 190 proof, non-beverage)	0.081
80.00	14	Polysorbate 80	80.00
0.16	15	Butylated hydroxyanisole (BHA)	0.16
0.66	16	Viosterol in corn oil (<i>syn.</i> , oleovitamin D; 1000 mD/g) (25% excess)	0.83
0.056	17	Vitamin A palmitate (1,500,000 Units/g)	0.056
10.00	18	Caramel (acid proof)	10.00
QS	19	Deionized purified water	QS to 1 L

MANUFACTURING DIRECTIONS

Product must not stand more than 1 week before filling. Avoid unnecessary exposure of product to light, air, and heat. Manufacture and store product under complete CO₂ protection. Avoid vigorous mixing. Charge glycerin and 210 mL purified water into a stainless steel, jacketed tank. Add, with mixing, in the following order: niacinamide, riboflavin-5'-phosphate sodium, methyl paraben, USP, benzoic acid, and saccharin sodium. Continue mixing, heat to 95 to 100°C, and hold to completely dissolve the ingredients. Add in calcium chloride portions, and stir until complete solution is obtained. Continue mixing, and cool to 70 to 75°C. Add ferrous gluconate with mixing and dissolve at 70 to 75°C. Check for the absence of undissolved material. Check volume; if necessary, replace lost purified water by heating with additional previously boiled purified water; QS to 750 mL. Cool with mixing to room temperature (25 to 30°C) while bubbling CO₂ gas through. Continue the CO₂ gas bubbling for balance of the process. Add and dissolve each ingredient

in this order: thiamine hydrochloride, pyridoxine hydrochloride, and ascorbic acid. Dissolve oil orange in ethyl alcohol, and add to mixture with stirring. Heat Polysorbate 80 to 50 to 60°C, and hold for approximately 10 minutes with slow mixing. Add and dissolve butylated hydroxyanisole. Mix slowly, and saturate with CO₂ while cooling to 25 to 30°C. Add and dissolve viosterol in corn oil and vitamin A palmitate, mixing well and continuing CO₂ gas bubbling. Add Polysorbate solution to main batch, and mix thoroughly. Rinse container with a portion of the main batch, and add. Heat 50 mL purified water to 35 to 40°C while bubbling CO₂ gas through. Add the caramel color. Mix well until uniform consistency is obtained. Add to main batch. Rinse container with a small quantity of purified water that has been previously saturated with CO₂ gas. Add to the main batch. Add purified water that has been previously saturated with CO₂ gas; QS to 1 L. Filter, without using a filter aid; cycle to achieve clarity. Maintain carbon dioxide cover.

Vitamin B-Complex, Vitamin A, Vitamin C, Vitamin D, and Mineral Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
61.00	1	Ascorbic acid (coated), EC	61.00
5.50	2	Calcium pantothenate	5.50
8.00 mcg	3	Cyanocobalamin	0.008
4.00	4	Copper sulfate, 5H ₂ O	4.00
1.70	5	Magnesium oxide (heavy)	1.70
10.00	6	Nicotinamide	10.00
0.575	7	Pyridoxin hydrochloride	0.575
0.16	8	Potassium iodide	0.16
2.30	9	Riboflavin	2.30
3.25	10	Thiamine mononitrate	3.25
24.00	11	Vitamin A palmitate (250,000 IU/g)	24.00
4.80	12	Vitamin D3 powder (100,000 IU/g)	4.80
2.20	13	Zinc sulfate, 7H ₂ O	2.20
19.265	14	Lactose monohydrate	19.265
25.00	15	Cellulose (microcrystalline) (Avicel™ PH102)	25.00
3.00	16	Povidone (PVP K-90)	3.00
6.50	17	Cellulose (microcrystalline) (Avicel™ PH102)	6.50
7.00	18	Crospovidone (Kollidon® CL)	7.00
1.00	19	Colloidal silicon dioxide (Aerosil® 200)	1.00
0.75	20	Magnesium stearate	0.75
3.00	21	Microcrystalline cellulose (powder)	3.00
—	22	Alcohol (absolute)	18.46

MANUFACTURING DIRECTIONS

Dissolve item 16 in item 22 using a stirrer. Dissolve item 3 while stirring to obtain a clear solution. Press items 10, 9, 7, 6, 2, 14, and 15 through a 500- μ m stainless steel sieve in a sifter. Load into mixer, and mix for 5 minutes at high speed. Knead the dry powder with binding solution while mixing at high speed for 3 minutes. After the addition is complete, scrape the sides and blades. Mix for an additional 2 minutes using a mixer and chopper at high speed. Check the end point of granulation. (The end point occurs when the granulation consists of few or no lumps.) If required, add an additional quantity of item 22, and record this extra quantity of item 22. Unload the wet granules in stainless steel trays for drying. Transfer the trays to an oven. Keep the door partially open. Switch on the oven, with air circulation, heater switched off, for 2 hours to evaporate alcohol. Close the door of the oven. Dry the granules at 55°C for 12.0 hours. After 4.0 hours

of drying, scrape the semidried granules to break up the lumps to promote uniform drying. Check the LOD (limit: 0.8 to 1.2%). If required, dry further at 55°C for 2 hours. Check the LOD. Grind the dried granules through a 1.25-mm sieve using a granulator set at medium speed. Load granules into the blender. Mix items 4 and 13 and 3.08 g of item 17 in a polyethylene bag. Mill through a Fitz mill using sieve number 1530-0030 (knives forward, medium speed). Collect in stainless steel drum. Add to blender. Sift items 11, 12, and 1 through a 630- μ m sieve. Add to blender. Sift items 5, 8, 18, 19, and 21 and 3.42 g of item 17 through a 500- μ m sieve. Add to blender. Mix for 5 minutes. Sift item 20 through a 250- μ m sieve. Mix a portion of the powder mix (~3.85 g) with sieved item 20. Add to the blender. Mix for 1 minute. Compress 185 mg per tablet using 7-mm, round, concave punches. Coat using a subcoat, a color coat, and a finishing coat (see Appendix).

Vitamin B-Complex, Vitamin A, Vitamin C, Vitamin D, and Vitamin E Pediatric Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
8333 IU	1	Vitamin A palmitate (1.7 M IU/g) (50% excess)	7.35
666 IU	2	Vitamin D (40 M IU/g) (Cholecalciferol)	0.021
75.00	3	Polysorbate 80 (Tween 80)	75.00
0.005	4	Lemon oil terpeneless	0.50
0.88	5	Vitamin E (oily) (α -tocopheryl acetate)	0.88
0.50	6	Edetate disodium (sodium EDTA)	0.50
83.33	7	Ascorbic acid (30% excess)	108.33
1.00	8	Saccharin sodium	1.00
2.50	9	Thiamine hydrochloride (50% excess)	3.75
16.66	10	Nicotinamide (5% excess)	17.50
0.833	11	Pyridoxine hydrochloride (5.6% excess)	0.88
2.00	12	Riboflavin sodium phosphate (7.9% excess as riboflavin)	2.16
700.00	13	Glycerin (glycerol)	700.00
250.00	14	Purified water	250.00

MANUFACTURING DIRECTIONS

This product is a microemulsion and is a thermolabile preparation. The temperature of the solution must not exceed 25°C at the time of processing. Add 200.0 g of purified water to the manufacturing vessel. Bubble nitrogen gas during all stages of the process. Charge items 6 to 12, one by one, into the manufacturing vessel while mixing. Check that all materials are dissolved completely. Load item 13 into the manufacturing vessel while mixing at slow speed. Mix for 5 minutes. Add item 3 in a separate stainless steel container. Mix items 1, 2, 4, and 5, one by one, using stirrer. Mix for 1 hour at slow speed. Add oil

phase preparation to the aqueous phase at a rate of 4 mL per minute while mixing at slow speed, and continue nitrogen gas bubbling throughout the process. Rinse the oil phase container with 50.0 g of nitrogen-bubbled and cooled purified water, and transfer the rinsing to the manufacturing vessel. Adjust the volume to 1.0 L using nitrogen-bubbled purified water. Mix for 15 minutes at slow speed. Check and record the volume and pH (limit: pH 2.8 to 4.2). Filter the solution through a Sartorius prefilter and 0.2- μ m membrane filter into receiving tank. Bubble with nitrogen gas for 15 minutes.

Vitamin B-Complex, Vitamin C, and Calcium Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
7.00	1	Thiamine mononitrate	7.00
5.00	2	Riboflavin	5.00
25.00	3	Nicotinamide	25.00
20.00	4	Pyridoxine hydrochloride	20.00
12.00	5	Calcium D-pantothenate	12.00
75.00	6	Calcium carbonate	75.00
164.00	7	Calcium glycerophosphate	164.00
400.00	8	Sodium bicarbonate	400.00
300.00	9	Tartaric acid (powder)	300.00
400.00	10	Sucrose (crystalline)	400.00
350.00	11	Sucrose (powder)	350.00
50.00	12	Kollidon® 30	50.00
10.00	13	Kollidon® 30	10.00
QS	14	Isopropanol	QS
550.00	15	Ascorbic acid (powder)	550.00
2.00	16	Riboflavin	2.00
5.00	17	Cyanocobalamin (gelatin-coated, 0.1%)	5.00
40.00	18	PEG-6000 (powder)	40.00
50.00	19	Kollidon® CL	50.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 12 with solution of item 19, and press with medium to high compressive force. 13 to 15, dry at 60°C with vacuum, mix with items 15 to 19. Compress 2.5 g using 20-mm planar punches.

Vitamin B-Complex, Vitamin C, and Ferrous Sulfate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Ferrous sulfate	300.00
15.00	2	Kollidon® 30	15.00
6.00	3	Kollidon® 30	6.00
QS	4	2-Propanol	QS
45.00	5	Thiamine mononitrate	45.00
10.00	6	Riboflavin	10.00
82.00	7	Pyridoxine hydrochloride	82.00
69.00	8	Nicotinamide	69.00
470.00	9	Ascorbic acid (powder)	470.00
690.00	10	Ludipress®	690.00
50.00	11	PEG-6000 (powder)	50.00
9.00	12	Aerosil® 200	9.00

MANUFACTURING DIRECTIONS

Granulate the mixture of items 1 to 2 with solution of items 3 and 4, pass through an 0.8-mm sieve, mix with items 5 to 12, and press with high compressive force (25 to 30 kN). Compress 1750 mg in 20-mm biplanar punches.

Vitamin B-Complex, Vitamin C, and Iron Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
QS	1	Glucose (liquid), NF	QS to 1 L
225.00	2	Purified water, USP	225.00
0.30	3	Methyl paraben	0.30
1.00	4	Acid benzoic, USP	1.00
5.00	5	Alcohol (ethanol; 190 proof, non-beverage), USP	5.00
10.00	6	Nicotinamide niacinamide (white powder), USP	10.00
10.00	7	Riboflavin; use riboflavin 5 phosphate sodium	1.64
2.00	8	Pyridoxine hydrochloride, USP	2.00
20.00	9	Ascorbic acid (white powder), USP	28.00
0.03	10	Dye	0.03
0.02	11	Dye	0.02
2.00	12	Thiamine hydrochloride (powder, regular), USP	2.40
2.00	13	D-pantothenyl alcohol	2.50
2.00 mcg	14	Vitamin B12 (cyanocobalamin, USP)	3.40 mg
200.00	15	Sucrose, NF	200.00
0.028 mL	16	Flavor	2.80 mL
QS	17	Hydrochloric acid	2.00 mL
QS	18	Carbon dioxide gas	QS

MANUFACTURING DIRECTIONS

This preparation is susceptible to oxidation and must be protected from air and sunlight at all times. Carbon dioxide must be used extensively to prevent oxygen from reacting with the materials. All purified water must be boiled prior to use for 10 minutes and cooled under CO₂ protection. Charge 100 mL of purified water into a suitably sized stainless steel tank. Add the riboflavin, nicotinamide, benzoic acid, and paraben. Rinse the tank down with 10 mL purified water, seal, and heat with mixing to 95°C. Continue mixing and heating for 15 minutes, until solution is complete. Commence cooling with continuous mixing. When the solution has cooled to 50 to 70°C, add and dissolve the sugar. Commence CO₂ protection when the temperature reaches 40°C. Slurry the ascorbic acid in 75.0 or 110.0 mL of CO₂-saturated purified water (use the smaller quantity *only* if using

a total of 225.0 mL water), and add to bulk solution when temperature has reached 25 to 35°C. Rinse the ascorbic acid vessel with 10.0 mL purified water, and add rinsing to bulk. Mix for at least 30 minutes. Dissolve thiamine and pyridoxine in 20.0 mL CO₂-saturated purified water, and add to bulk solution at 25 to 35°C. Add 10.0 mL CO₂-saturated purified water, to the D-pantothenyl alcohol and warm on a water bath until solution is complete. Add vitamin B12, and mix until dissolved. Add and dissolve dyes. Add this solution to the bulk solution, and mix thoroughly. Mix flavor with 95% of alcohol, and add to the bulk solution. Rinse the container with the remaining alcohol, and add to the bulk with vigorous agitation. Check pH (range: 3.0 to 3.3). Use hydrochloric acid to adjust, if necessary. Adjust the final volume with liquid glucose. Filter through suitable medium until clear and bright.

Vitamin B-Complex, Vitamin C, and Iron Syrup

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/L (g)
QS	1	Sorbitol solution, USP	QS to 1 L
QS	2	Purified water, USP	225.00
0.20	3	Methyl paraben	0.20
0.20	4	Propyl paraben, NF	0.02
2.00	5	Nicotinamide niacinamide (white powder), USP	10.00
10.00	6	Riboflavin; use riboflavin 5 phosphate sodium	1.64
10.00	7	Iron sulfate (ferrous sulfate; granular), USP	10.00
3.60	8	Saccharin sodium (powder), USP	3.60
2.00	9	Pyridoxine hydrochloride, USP	2.00
25.00	10	Ascorbic acid (white powder), USP	28.00
0.03	11	Dye	0.030
0.02	12	Dye	0.020
2.00	13	Thiamine hydrochloride (powder, regular), USP	2.40
2.00	14	D-pantothenyl alcohol	2.50
2.0 mcg	15	Vitamin B12 cyanocobalamin, USP	3.40 mg
1.00	16	Flavor	1.00
10.00	17	Propylene glycol, USP	10.00
QS	18	Hydrochloric acid	2.00 mL
—	19	HyFlo filter aid	1 g
QS	20	Carbon dioxide gas	QS

MANUFACTURING DIRECTIONS

This preparation is susceptible to oxidation and must be protected from air and sunlight at all times. Carbon dioxide must be used extensively to prevent oxygen from reacting with the materials. All purified water must be boiled prior to use for 10 minutes and cooled under CO₂ protection. Charge 950 g of sorbitol solution into a jacketed stainless steel tank and heat to 95 to 100°C. Heat 250 mL of purified water to boiling for 10 minutes, and bubble CO₂ into it while cooling to room temperature. Add, with stirring, the parabens, niacinamide, and riboflavin 5 phosphate sodium. Rinse the container with 5 mL of water. Stir well. Mix until solution is obtained, and check the clarity. Remove the source of heat from the vessel. Thoroughly deoxygenate the liquid by bubbling CO₂ through the liquid and allow to cool to 50 to 60°C. Heat 15 mL of water to 70°C, saturate with CO₂, and dissolve saccharin sodium (item 8) and pyridoxine hydrochloride in 5 mL of water; add to the main bulk. Rinse the container with 2.5 mL of water. Cool the solution to 30°C with CO₂ protection. Dissolve ascorbic acid in 120 mL of water. Rinse the container with 5 mL of water.

Dissolve dyes in 3 mL of water. Rinse the container with 2 mL of water. Mix dye solution with ascorbic acid solution. Add this to the main bulk with stirring. Dissolve thiamine in 30 mL of water, and add to the main bulk. Rinse the container with 2.5 mL of water. Add 10 mL of water to the D-pantothenyl, and warm up on a water bath until in solution. Add this mixture to the main bulk. Rinse the container with 2.5 mL of water. Dissolve vitamin B12 in 12.5 mL of water and add to the main bulk. Rinse the container with 2.5 mL of water. Mix flavor with 7.5 g of propylene glycol until mixture is homogeneous, and add to the main bulk. Rinse the container with 2.5 g of propylene glycol, and add to the main bulk with vigorous agitation. Check pH (range: 3.0 to 3.3). Use hydrochloric acid to adjust, if necessary. Adjust the volume of the product with sorbitol solution, and mix for 30 minutes to ensure homogeneity. Add the HyFlo filter aid and mix. Filter the liquid through a filter press previously washed in purified water. Transfer the clear filtrate into a clean closed vessel. Mix for 15 minutes while bubbling CO₂ gas.

Vitamin B-Complex, Vitamin C, and Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Niacinamide, (white powder), USP	100.00
750.00	2	Ascorbic acid; use sodium ascorbate (microcrystalline), USP	843.65
20.00	3	Calcium pantothenate, USP	30.00
10.00	4	Riboflavin, USP	10.00
5.00	5	Pyridoxine hydrochloride, USP	5.25
40.00	6	Povidone, USP	40.00
68.00	7	Anhydrous isopropyl alcohol	68.00
15.00	8	Thiamine mononitrate (powder), USP	15.75
24.79	9	Vitamin E, USP, <i>d,l</i> - α -tocopheryl acid succinate	33.71
150.00 mcg	10	Folic acid (powder), USP	0.18
5.00	11	Magnesium stearate	5.00
40.00	12	Cellulose (microcrystalline), NF	40.00
4.00 mcg	13	Vitamin B12; use cyanocobalamine powder in gelatin (1000 μ g/g)	4.20

MANUFACTURING DIRECTIONS

Avoid unnecessary exposure to light and moisture. Mill the nicotinamide and the sodium ascorbate through a 600- μ m screen fitted to a Fitz mill, or similar (impact forward, high speed). Load into a suitable mass mixer. Load calcium pantothenate, riboflavin, and pyridoxine hydrochloride into the mass mixer. Dry blend for 5 minutes. Dissolve Povidone in alcohol (~84 mL) in a separate container. While mixing the blended powders add the Povidone solution. Continue to mix until a satisfactory granule mass is obtained. If required, use additional alcohol. Granulate through a Fitz mill, or similar, using a 5/8-inch band (15.88-mm aperture or similar) or a 4.76-mm screen with knives forward at slow speed. Dry the granulation at 49°C to less than 1.5% LOD. Sift the dry granulation through a 1.19-mm screen. Pass remaining

coarse granules through a #2 band (1.59-mm aperture or similar) using a Fitz mill, or similar (knives forward, medium speed). Blend together the thiamine mononitrate, vitamin E, folic acid, magnesium stearate, and a portion of the microcrystalline cellulose. Mill blended powders through a 600- μ m screen (impact forward, high speed). Care must be taken to prevent losses. Load half of the base granulation, the balance of the microcrystalline cellulose, and the powder blend into a suitable blender. Blend for 5 minutes. Add balance of base granulation, and blend for 15 minutes. Do not mill cyanocobalamine. Blend together by hand the cyanocobalamine with a portion of the blended powders. Return to the blender, and blend for 15 minutes. Compress using ovaloid-shaped punches. Seal tablets with a subcoat, and then apply color coat and finishing coating.

Vitamin C and Calcium Carbonate Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Calcium; use calcium carbonate	315.00
450.00	2	Sodium bicarbonate/tartaric acid (powder)	450.00
600.00	3	Kollidon® 30	600.00
35.00	4	Kollidon® 30	35.00
200.00	5	Isopropanol	200.00
400.00	6	Sucrose (crystalline)	400.00
500.00	7	Ascorbic acid (crystalline, with excess)	550.00
120.00	8	Kollidon® CL	120.00
60.00	9	PEG-6000 (powder)	60.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 3 with a solution of items 4 and 5, mix with item 6, and dry. Add items 7 to 9, and

press with high compressive force at a maximum atmospheric relative humidity of 30%. Compress 2500 mg in 20-mm biplanar punches.

Vitamin C and Vitamin E Lozenges

Bill of Materials			
Scale (mg/lozenge)	Item	Material Name	Quantity/1000 Lozenges (g)
100.00	1	Ascorbic acid (crystalline)	100.00
50.00	2	Vitamin E acetate (dry powder, SD 50)	100.00
400.00 g	3	Dextrose	400.00
4.00 g	4	Kollidon® 90 F	4.00
25.00 g	5	Isopropanol	25.00
6.00 g	6	PEG-6000 (powder)	6.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 to 4 with isopropanol, dry, pass through an 0.8-mm sieve, mix with item 6, and press

with high compressive force. Compress 600 mg using 12-mm biplanar punches.

Vitamin C Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Ascorbic acid: 222.20 mg ascorbic acid and 312.50 mg sodium ascorbate microcrystalline	500.00
850.00	2	Sorbitol (granular)	850.00
100.00	3	Lactose (120 mesh)	100.00
3.30	4	FD&C Yellow Dye No. 5 lake	3.30
82.90	5	Cellulose (microcrystalline), NF (Avicel™ PH101)	82.90
11.60	6	Silica gel	11.60
8.29	7	Flavor	8.29
0.50	8	Flavor	0.50
8.29	9	Sodium cyclamate	8.29
33.20	10	Magnesium stearate	33.20

MANUFACTURING DIRECTIONS

Pass the ascorbic acid, sodium ascorbate, sorbitol, lactose, FD&C Yellow Dye, microcrystalline cellulose, silica gel, flavors, and sodium cyclamate through a 420- μ m screen. Using a comminuting mill, pass the coarse granules through

a 420- μ m screen (knives forward, medium speed). Transfer milled materials to a suitable blender, and blend for 5 minutes. Screen the magnesium stearate by hand through an 840- μ m screen, and transfer to blender. Mix for 1 minute. Compress using 18-mm standard concave punches.

Vitamin C Chewable Tablets

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
422.00	1	Ascorbic acid (powder)	422.00
283.00	2	Microcrystalline cellulose	283.00
130.00	3	Sucrose (powder)	130.00
80.00	4	Sucrose (crystalline)	80.00
24.00	5	Kollidon® VA 64	24.00
24.00	6	Cyclamate sodium	24.00
20.00	7	PEG-6000 (powder)	20.00
12.00	8	Orange flavor and strawberry flavor	12.00
2.00	9	Aerosil® 200	2.00
1.00	10	Saccharin sodium	1.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm sieve, and press into tablets with medium to high compressive force.

Compress 250 mg (for 100 mg strength), 1250 mg (for 500 mg strength), or 2500 mg (for 500 mg strength).

Vitamin C Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Ascorbic acid (crystalline)	500.00
1100.00	2	Sorbitol (crystalline)	1100.00
200.00	3	Sucrose (crystalline)	200.00
200.00	4	Sucrose (powder)	200.00
300.00	5	Dextrose	30.00
100.00	6	PEG-6000 (powder)	100.00
10.00	7	Magnesium stearate	10.00
10.00	8	Aerosil® 200	10.00
1.00	9	Saccharin sodium	1.00
10.00	10	Cyclamate sodium	10.00
30.00	11	Orange flavor	30.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with medium to high compressive force. Compress 2080 mg using 20-mm biplanar punches.

Vitamin C Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Ascorbic acid (crystalline)	100.00
450.00	2	Sodium ascorbate (crystalline)	450.00
264.00	3	Sorbitol (crystalline)	264.00
200.00	4	Sucrose (crystalline)	200.00
200.00	5	Sucrose (powder)	200.00
300.00	6	Dextrose	300.00
60.00	7	PEG-6000 (powder)	60.00
3.00	8	Magnesium stearate	3.00
4.00	9	Aerosil® 200	4.00
1.00	10	Saccharin sodium	1.00
10.00	11	Cyclamate sodium	10.00
20.00	12	Orange flavor	20.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with medium to high compressive force. Compress 1295 mg using 16-mm biplanar punches.

Vitamin C Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
6.70	1	Anhydrous silica (colloidal) (Aerosil® 200)	6.70
40.00	2	Cellulose (microcrystalline) (Avicel™ PH101)	40.00
6.50	3	Aspartame	6.50
170.00	4	Ascorbic acid (coated), EC	170.00
10.50	5	Orange flavor (dry)	10.50
13.00	6	Carmellose sodium (sodium CMC 7 MFD)	13.00
2.80	7	Orange dye	2.80
470.00	8	Dextrates, NF	470.00
19.50	9	Magnesium stearate	19.50
13.00	10	Stearic acid (fine powder)	13.00
160.00	11	Sorbitol (powder)	160.00
388.00	12	Sodium ascorbate (granular)	388.00

MANUFACTURING DIRECTIONS

Processing should be done in a controlled temperature and humidity area (limit: relative humidity, 40 to 50%; temperature, 20 to 25°C). Mix items 2 and 7 in a polyethylene bag for 1 to 2 minutes. Sift twice through a 250-µm sieve. Collect in a polyethylene bag, and check the uniformity of dispersion. If required, sift again. Mix items 3, 5, and 6 in a polyethylene bag for 1 to 2 minutes. Sift once through a 250-µm sieve. Add to the first step, and mix for 1 to 2 minutes. Sift items 8, 11, 4, and 12 once through a 1000-µm sieve, and collect in a stainless steel drum. Add the sieved materials from the above steps to the

stainless steel drum. Mix in a drum blender for 2 to 3 minutes. Mix items 10, 9, and 1 in a polyethylene bag for 1 to 2 minutes. Sift twice through a 500-µm sieve. Add 25.0 to 30.0 g of granules to the lubricant mixture. Mix for 1 to 2 minutes. Add this mixture to the granules. Mix in a drum blender for 1 minute. Check the moisture content (limit: moisture content NMT 3.5%). Check temperature and humidity before beginning compression (limit: relative humidity, 40 to 50%; temperature, 20 to 25°C). Compress 1300 mg per tablet using 16-mm punches. Fill appropriate amounts for lower strength (e.g., 100 mg tablets in 10-mm punches).

Vitamin C Chewable Tablets with Dextrose

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Ascorbic acid (crystalline); use ascorbic acid (coated, 97.5%), EC	110.00
500.00	2	Dextrose	500.00
4.00	3	Kollidon® 90 F	4.00
30.00–50.00	4	Water and/or isopropanol	30.00–50.00
6.00	5	PEG-6000 (powder)	6.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 and 2 with solution of items 4 and 5 (in a fluidized bed), sieve, add item 6, and press with high compression force. Compress 620 mg in 12-mm

biplanar punches. If no fluidized bed is available, use of water as a granulation solvent should be avoided. The use of coated ascorbic acid does not increase the stability.

Vitamin C Chewable Tablets with Fructose

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
120.00	1	Ascorbic acid (powder)	120.00
500.00	2	Fructose	500.00
200.00	3	Ludipress®	200.00
100.00	4	Avicel™ PH101	100.00
15.00	5	Kollidon® VA 64	15.00
4.00	6	Aerosil® 200	4.00
35.00	7	PEG-6000 (powder)	35.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with high compression force. Compress 970 mg in 12-mm biplanar punches.

Vitamin C Chewable Tablets with Sucrose

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Ascorbic acid	500.00
850.00	2	Sucrose, crystalline	850.00
575.00	3	Avicel™ PH 101	575.00
60.00	4	Kollidon® VA 64	60.00
15.00	5	Magnesium stearate	15.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with medium compressive force. Compress 2000 mg in 20-mm biplanar punches.

Vitamin C Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
100.00	1	Ascorbic acid (white powder), USP	100.00
979.00	2	Propylene glycol, USP	979.00

MANUFACTURING DIRECTIONS

Keep under CO₂ protection at all times. Avoid contact with iron. Use stainless steel or glass-lined equipment only. Load 868 g propylene glycol into a glass-lined or suitable stainless steel jacketed tank. While mixing, heat to 70 to 80°C. Bubble CO₂ gas into the propylene glycol from the bottom of the tank. Add and dissolve the ascorbic acid into the propylene glycol with a minimum of stirring under CO₂

protection. When the ascorbic acid is in solution, immediately cool to approximately 25°C while continuing to mix. Also, while cooling, change adding CO₂ from the bottom of the tank to adding it at the top of the tank. QS to 1 L, using propylene glycol, and mix for at least 10 minutes. Use a prefilter pad and a lint-free filter paper; recirculate the product through the filter press until sparkling clear.

Vitamin C Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1000.00	1	Vitamin C (as ascorbic acid)	1000.00
800.00	2	Tartaric acid (fine crystals)	800.00
1000.00	3	Sodium bicarbonate	1000.00
0.50	4	Riboflavin	0.50
20.00	5	Saccharin sodium	20.00
20.00	6	Sodium chloride (milled)	20.00
50.00	7	Lime flavor	50.00
1709.50	8	Sugar (fine crystals)	1709.50
QS	9	Alcohol	QS

MANUFACTURING DIRECTIONS

All operations must be carried out at a relative humidity of less than 40% at 25°C. *Active substance granulate*: If saccharin sodium is lumpy, sieve it by means of a centrifugal granulator (1 mm) or a 3-mm band sieve. Suck into the mixer the entire amount of sugar, ascorbic acid, tartaric acid, and saccharin sodium (previously sieved, if required), together with 1st part sieved sodium bicarbonate (open filter, closed bypass; jacket temperature of 40°C); backflash filter twice, evacuate to ~800 mbar, and close filter. Mix with mixer for approximately 10 minutes (jacket temperature 40°C) at a speed of 50 rpm. Turn off the mixer, and evacuate to 10 mbar (open filter, closed bypass; jacket temperature of 40°C). Separately dissolve or suspend riboflavin in alcohol. Suck this granulating liquid into the evacuated vessel at a mixer speed of 30 rpm (closed filter, closed bypass; jacket temperature of 40°C). With jacket heating turned off, granulate up to a product temperature of 60°C at a mixer speed of 110 rpm (time required is approximately 20 to 25 minutes). At a jacket temperature of 56°C and a mixer rotation speed of approximately 15 rpm, dry for 2 to 5 minutes (closed filter, open bypass). When dust develops in the course of further

drying, close the bypass and open the filter. At a mixer speed of 20 rpm and interval setting (2 minutes/15 seconds), continue the drying at a jacket temperature of approximately 58°C and vacuum of 10 mbar until a total drying time of 10 to 20 minutes is reached. Sieve the active substance granulate by sucking it by means of vacuum at a jacket temperature of approximately 59°C and a mixer speed of 20 rpm through a Buehler universal mill (1.5-mm screen) directly into a suitable container. Preferable relative humidity of the active substance is less than 10%. Sieve milled sodium chloride and lime flavor through a round hand sieve (1 mm) with a diameter of approximately 38 cm; add to sieved sodium carbonate (2nd part) in a mixing drum, and mix (e.g., tumble mix, 19 rpm for 10 minutes). Combine this dry mix (sucked by vacuum) with the active substance granulate. Finally, add the remaining sieved and lump-free sodium bicarbonate (3rd part). Mix the mixture that is ready for compression for 45 minutes. The preferable relative humidity of the mixture is less than 20%. In a suitable rotary tablet press, compress effervescent tablets with a weight of 4600 mg and a hardness of 8 kpi.

Vitamin C Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Ascorbic acid, (powder)	112.00
200.00	2	Sorbitol (instant)	200.00
1000.00	3	Anhydrous citric acid	1000.00
587.00	4	Sodium bicarbonate	587.00
65.00	5	PEG-6000 (powder)	65.00
10.00	6	Lemon flavor	10.00
25.00	7	Cyclamate sodium	25.00
1.00	8	Saccharin sodium	1.00

MANUFACTURING DIRECTIONS

Dry the sodium bicarbonate for 1 hour at 100°C, mix with the other components, pass all through an 0.8-mm sieve,

and press with high compressive force at a maximum atmospheric relative humidity of 30%. Compress 2050 mg in 20-mm biplanar punches.

Vitamin C Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1000.00	1	Ascorbic acid (crystalline)	1000.00
800.00	2	Sorbitol (crystalline)	800.00
150.00	3	Anhydrous citric acid	150.00
660.00	4	Sodium bicarbonate	660.00
80.00	5	PEG-6000 (powder)	80.00
QS	6	Lemon flavor	QS
QS	7	Cyclamate sodium	QS
QS	8	Saccharin sodium	QS

MANUFACTURING DIRECTIONS

Dry the sodium bicarbonate for 1 hour at 100°C, mix with the other components, pass all through an 0.8-mm sieve,

and press with high compressive force at a maximum atmospheric relative humidity of 30%. Compress 2690 mg in 20-mm biplanar punches.

Vitamin C Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Sodium hydrogen carbonate	500.00
430.00	2	Tartaric acid	430.00
8.00	3	Kollidon® 25	8.00
0.20	4	2-Propanol	200.00 mg
550.00	5	Ascorbic acid (crystalline)	550.00
660.00	6	Sucrose	660.00
67.00	7	PEG-6000 (powder)	67.00
67.00	8	Dextrose (powder)	67.00
10.00	9	Orange flavor	10.00
1.00	10	Saccharin sodium	1.00

MANUFACTURING DIRECTIONS

Granulate mixture of items 1 and 2 with solution of items 2 and 3, pass through a 0.5-mm sieve, and dry at 60°C. Dry mixture of items 5 and 6 at 60°C. Mix together with

the previous granules and with items 7 to 10. At a maximum atmospheric relative humidity of 30%, press to effervescent tablets. Compress 2300 mg in 20-mm biplanar punches.

Vitamin C Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Ascorbic acid (coated)	104.00
2.40	2	Anhydrous colloidal silica (Aerosil® 200)	2.40
60.00	3	Cellulose (microcrystalline) (Avicel™ PH102)	60.00
0.13	4	FD&C Yellow Dye No.10 lake	0.13
37.00	5	Lactose (spray-dried)	37.00
3.20	6	Glyceryl behenate (glyceryl monostearate)	3.20
2.40	7	Stearic acid (fine powder)	2.40
1.00	8	Magnesium stearate	1.00

MANUFACTURING DIRECTIONS

Processing should be done under controlled temperature and humidity (limit: relative humidity, 40 to 50%; temperature, 20 to 25°C). Mix items 5 and 4 in a polyethylene bag for 1 to 2 minutes. Sift twice through a 630-µm sieve. Collect in a polyethylene bag. Check the uniformity of dispersion. If required, sift again. Sift item 3. Sift mixture from first step and item 2 through a 630-µm sieve. Load into a drum blender. Sift item 4 through a 630-µm sieve. Load into the mix in the drum blender. Mix items 6, 7,

and 8 in a polyethylene bag for 1 to 2 minutes. Sift through a 250-µm sieve. Collect in a polyethylene bag. Add 13.33 to 20.00 g of granules to the lubricant mixture. Mix for 1 to 2 minutes. Add this to the mix in a stainless steel drum blender. Mix in a drum blender for 2 minutes. Check the temperature and humidity before beginning compression (limit: relative humidity, 40 to 45%; temperature, 20 to 25°C). Compress 210 mg in 8-mm round concave punches.

Vitamin C Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Ascorbic acid (powder)	100.00
232.00	2	Ludipress®	232.00
1.00	3	Magnesium stearate	1.00

MANUFACTURING DIRECTIONS

Mix all components, sieve, and press into 335-mg tablets.
Compression force affects disintegration time.

Vitamin C Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Ascorbic acid (powder)	200.00
231.00–256.00	2	Ludipress®	231.00–256.00
25.00	3	Kollidon® VA 64	25.00
15.00	4	Kollidon® CL	15.00
1.20	5	Aerosil® 200	1.20
2.50	6	Magnesium stearate	2.50

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm screen, and press with medium compression force (18 kN). Compress 499 mg in 12-mm biplanar punches.

Vitamin E and Benzocaine Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
50.00	1	Vitamin E acetate	50.00
20.00	2	Benzocaine	20.00
50.00	3	Lutrol F 127	50.00
250.00	4	Cremophor (relative humidity, 40%)	250.00
2.00	5	Sorbic acid	2.00
628.00	6	Water	628.00

MANUFACTURING DIRECTIONS

Dissolve sorbic acid and benzocaine in water at 60°C, slowly add the heated mixture of vitamin E acetate and Cremophor at a relative humidity of 40% and temperature

of 60 to 65°C. Cool the clear solution to about 5°C, and dissolve Lutrol F 127 to obtain a clear, colorless, viscous liquid.

Vitamin E Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Vitamin E acetate (SD 50)	200.00
493.00	2	Ludipress®	493.00
390.00	3	Sorbitol (crystalline)	390.00
100.00	4	Mannitol	100.00
400.00	5	Dicalcium phosphate (granulated with 5% Kollidon® 30)	400.00
7.00	6	Aerosil® 200	7.00
3.00	7	Magnesium stearate	3.00

MANUFACTURING DIRECTIONS

Mix all components, pass through an 0.8-mm screen, and press with high compressive force. Compress 711 mg in 12-mm biplanar punches.

Vitamin E Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
150.00	1	Vitamin E acetate (dry powder, 50%)	300.00
300.00	2	Sorbitol	300.00
6.00	3	Aerosil® 200	6.00
0.20	4	Saccharin sodium	0.20
6.00	5	Magnesium stearate	6.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with high compressive force. Compress 620 mg in 12-mm biplanar punches.

Vitamin E Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Vitamin E acetate (dry powder, SD 50)	800.00
790.00	2	Ludipress®	790.00
20.00	3	Aerosil® 200	20.00
QS	4	Flavors	QS

MANUFACTURING DIRECTIONS

Pass all components through a 0.5-mm sieve, mix, and press with high compressive force. Compress 1665-mg tablets in 20-mm biplanar punches.

Vitamin E Concentrate, Water-Miscible

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
105.00	1	Vitamin E acetate	105.00
250.00	2	Cremophor (relative humidity, 40%)	250.00
QS	3	Preservative	QS
QS	4	Water	QS to 1 L

MANUFACTURING DIRECTIONS

Heat the mixture of items 1 and 2 and solution of item 3 in item 4 separately to about 65°C, and slowly add to the well-stirred solution to obtain a clear, colorless liquid that is miscible with water.

Vitamin E Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
50.00	1	Vitamin E acetate	50.00
160.00	2	Cremophor (relative humidity, 40%)	160.00
QS	3	Preservative	QS
QS	4	Water	QS to 1 L

MANUFACTURING DIRECTIONS

Heat mixture of items 1 and 2 and solution of item 3 in 4 to about 65°C, and add them slowly to obtain a clear or lightly opalescent, colorless liquid.

Vitamin E Gel-Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
100.00	1	Vitamin E acetate	100.00
150.00	2	Propylene glycol (Pharma)	150.00
200.00	3	Lutrol F 127	200.00
550.00	4	Water	550.00

MANUFACTURING DIRECTIONS

Mix vitamin E acetate with propylene glycol, and add the water. After cooling to about 6°C, slowly dissolve Lutrol F 127 in the well-stirred mixture. Maintain cool until the air bubbles escape to obtain a turbid white gel at temperatures from 20 to 50°C with viscosity at 25°C of about 120,000 mPa.

Vitamin E Softgel Capsules

Bill of Materials			
Scale (mg/Capsule)	Item	Material Name	Quantity/1000 Capsules (g)
400.00	1	Vitamin E preparation, USP	400.00
25.00	2	Soyabean oil, USP	25.00
QS	3	Gelatin mass (clear)	QS

MANUFACTURING DIRECTIONS

Weigh items 1 and 2 and transfer into a suitable stainless steel container; mix for a minimum of 1 hour. Transfer

into medicine tanks through a #80- to #100-mesh stainless steel screen. Encapsulate 425 mg of mixture into size 7.5 oval capsules using clear gelatin mass.

Vitamin E Solution with Ethanol

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/L (g)
0.10	1	I. Vitamin E acetate	0.10
4.00–5.00	2	Cremophor, EL	4.00–5.00
570.00	3	II. Water	570.00
380.00	4	Ethanol (96%)	380.00

MANUFACTURING DIRECTIONS

Heat mixture of item 1 and 2 to about 60°C, stir well, and slowly add the warm solvent mixture of items 3 and 4 to obtain a clear, colorless liquid of low viscosity.

Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Vitamin E acetate (dry powder, SD 50)	100.00
140.00	2	Mannitol	140.00
140.00	3	Tabletose®	140.00
15.00	4	Kollidon® VA 64	15.00
2.00	5	Magnesium stearate	2.00
10.00	6	Aerosil® 200	10.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with high compressive force. Compress 410 mg in 12-mm biplanar punches.

Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Vitamin E acetate (dry powder, SD 50)	100.00
300.00	2	Sorbitol (crystalline)	300.00
3.00	3	Magnesium stearate	3.00
3.00	4	Aerosil® 200	3.00

MANUFACTURING DIRECTIONS

Pass all components through an 0.8-mm sieve, mix, and press with high compressive force. Compress 413 mg in 12-mm biplanar punches.

Zinc Oxide Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
7.00	1	Magnesium aluminum silicate	7.00
641.00	2	Water	641.00
7.00	3	Unimulse C	7.00
30.00	4	Propylene glycol	30.00
30.00	5	Eucalyptus oil	30.00
30.00	6	Lanolin oil	30.00
50.00	7	Dimethicone (350 cS)	50.00
50.00	8	Benzoate alcohol (C12–C15)	50.00
100.00	9	Polysorbate 80	100.00
50.00	10	Zinc oxide	50.00
10.00	11	Corn starch	10.00
QS	12	Preservatives	QS

MANUFACTURING DIRECTIONS

Slowly add item 1 to the water, agitating with maximum shear until smooth. Add items 3 and 4, mixing each time

until uniform. Mix items 5 to 10 until uniform, and mix with other portions until uniform. Add items 11 and 12, and mix until smooth.

Zinc Oxide Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
120.00	1	Cetearyl alcohol and PEG-40 castor oil and sodium cetearyl sulfate	120.00
180.00	2	Petrolatum	180.00
60.00	3	Oleayl oleate	60.00
60.00	4	Mineral oil (light)	60.00
100.00	5	Zinc oxide	100.00
QS	6	Water	QS
10.00	7	Propylene glycol, diazolidinyl urea, methyl paraben, and propyl paraben	10.00

MANUFACTURING DIRECTIONS

Mix and heat items 1 to 5 to 70 to 75°C. Mix and heat items 6 and 7 to 70 to 75°C. While stirring, add second mixture to first mixture. Begin cooling, and continue stirring until batch reaches 30°C, then homogenize.

Zinc Pyrithione Shampoo

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/1000 Tablets (g)
547.50	1	Deionized water	547.50
7.50	2	Hydroxyethylcellulose	7.50
347.00	3	TEA-lauryl sulfate	347.00
43.00	4	PEG-20 lanolin alcohol ether	43.00
20.00	5	Glycol stearate	20.00
15.00	6	Cocamide MEA	15.00
10.00	7	Zinc pyrithione (48%)	20.00
QS	8	Fragrance, preservative	QS

MANUFACTURING DIRECTIONS

Add item 2 to the water and mix. In a separate vessel, combine items 3 to 5, heat to 80°C, and mix. Cool to 50°C. Add items 6 and 7, and mix. Add this mixture to mixture of item 2. Cool to 40°C, and add item 8.

Zinc Undecylenate Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
7.50	1	Magnesium aluminum silicate	7.50
487.50	2	Deionized water	487.50
100.00	3	Sorbitol 70%	100.00
10.00	4	Polysorbate 80	10.00
200.00	5	Zinc undecylenate	200.00
50.00	6	Caprylic acid	50.00
30.00	7	C12–C15 Benzoate alcohol	30.00
15.00	8	Polysorbate 80	15.00
20.00	9	C18–C36 acid	20.00
80.00	10	Glyceryl stearate and PEG-100 stearate	80.00
QS	11	Preservatives	QS

MANUFACTURING DIRECTIONS

Slowly add item 1 in the water, mixing with maximum available shear until smooth. Add items 2 to 5 in order, mixing each until uniform. Avoid incorporating air; heat

with stirring to 70 to 75°C. Heat items 6 to 10 separately to 70 to 75°C, and add to the above mixture with mixing while cooling; fill at 45 to 50°C.

Zirconium Oxide Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
15.00	1	Magnesium aluminum silicate	15.00
3.00	2	Carboxymethyl cellulose sodium (medium viscosity)	3.00
796.50	3	Water	796.50
40.00	4	Zirconium oxide	40.00
50.00	5	Propylene glycol	50.00
80.00	6	Isopropyl alcohol	80.00
15.00	7	Benzocaine	15.00
0.50	8	Menthol	0.50
QS	9	Preservative	QS

Manufacturing Directions

Dry blend items 1 and 2, and slowly add them to the water while agitating with maximum shear until smooth. Add items 4 and 5 and then items 6 to 9; mix.